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Proceedings of the Royal Society of Medicine Vol. 45 51

Section of Anæsthetics

President—JOHN GILLIES, C.V.O., M.C., M.R.C.P.Ed., F.R.C.S.Ed., F.F.A.R.C.S.

[*November* 2, 1951]

The Present Position of Anæsthesia for Thoracic Surgery

By E. JOAN MILLAR, M.B., B.S., F.F.A.R.C.S.

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THORACIC surgery probably provides the most fascinating work for an anæsthetist. The variety and volume of material are well shown by the following data from the clinics with which I am associated. During the first nine months of 1951 our operative work has included 243 thoracoplasties and 61 resections for pulmonary tuberculosis, 153 radical resections for bronchiectasis (pneumonectomy 17, lobectomy or segmental resection 136), 38 resections for bronchial carcinoma, 67 cardiovascular operations (mitral valvulotomy 40, pericardectomy 5, congenital hearts 12, cardiac ischæmia, aneurysm, &c. 10). In addition there were a number of diaphragmatic herniæ, œsophageal resections, thymectomies, &c. Many thoracic investigations also entail close co-operation from the anæsthetist, including the endoscopic examinations, bronchographies, angiocardiographies, and cardiac catheterizations.

INVESTIGATIONS

Bronchography in children should be the responsibility of the anæsthetist. Its object is not only to demonstrate bronchiectasis, but to produce a series of bronchograms outlining each segment of the lungs. This is especially important in bilateral disease where it is essential to decide whether or not sufficient healthy segments can be conserved. It is our practice to bring these children into hospital some days or even weeks before the examination in order to prepare them thoroughly by postural coughing and respiratory exercises. The investigation must be made pleasant for the child as it is often necessary to have three sets of bronchograms—one taken before operation and two post-operatively. Basal narcosis with avertin is used together with a suitable dose of atropine. Since the majority of these children have sputum which may prevent the satisfactory filling with Lipiodol of the whole bronchial tree, a preliminary bronchoscopic aspiration is performed under light general anæsthesia, the larynx and trachea having first been cocainized. This examination also excludes the presence of a foreign body or of granulation tissue. The largest bore, plain, endotracheal tube which will comfortably fit the glottis is then passed and calm anæsthesia is re-established. A satisfactory diagnosis can only be made from radiographs showing two views of each lung; thus, as a general rule, pictures are taken in the right lateral, left oblique, and antero-posterior positions. When a satisfactory plane of anæsthesia has been reached, lipiodol is injected through a fine-bore catheter introduced through the endotracheal tube. The agents used for anæsthesia are a matter of personal choice, but a simple technique with open ether will give satisfactory results. Before aspirating the lipiodol and secretions, the films must be examined carefully to see that each segment is properly outlined. In very small children it may sometimes be difficult to maintain an efficient airway when the lipiodol catheter has been introduced into the endotracheal tube; in this case the endotracheal tube may be dispensed with, and the oil injected through a fine gum-elastic catheter directly into the trachea. These details may seem elementary, but the results of surgical resection for bronchiectasis depend largely on accurate localization of the disease.

Similarly *œsophagoscopy* in young children requires careful anæsthesia, especially in those with œsophageal ulceration associated with hiatus hernia. Despite vigorous preparation these children readily tend to regurgitate; anæsthesia should be induced in a foot-down position and intubation carried out before œsophagoscopy is attempted.

Angiocardiography is a frightening procedure for a child. Alarming bronchospasm may follow the injection of diodrast; for this reason the child should first be intubated. A preliminary injection of procaine through the intravenous cannula will facilitate the rapid injection of diodrast.

Basal narcosis with avertin can be used for *cardiac catheterization* in young children when samples of blood are required for gas analysis. An initial dose of 100 mg. per kg. body-weight is given and supplemented by doses of 20–40 mg. per kg., should anæsthesia begin to wear off during the procedure. A liberal injection of procaine at the site of introduction of the cardiac catheter is necessary.

Bronchospirometry is another investigation of particular interest to the anæsthetist. In borderline cases requiring lung resection it may be necessary to assess the pulmonary and ventilatory function of each lung separately if operation is not to make them respiratory cripples. Recently we have carried out differential spirometry using the double-lumen Carlens (1949) tube. Good topical anæsthesia is essential, and in order to carry out the tests efficiently we have used atropine as the sole premedication. With this technique we have been able to measure the vital capacity, the oxygen consumption and the maximum breathing capacity of each lung both at rest and after exercise.

Special Problems of Anæsthesia for Major Thoracic Surgery

It is essential that the anæsthetist understands clearly what happens to the lungs and mediastinum when the chest wall is widely opened. Nosworthy (1941, 1951) has written excellent descriptive articles on this subject, explaining the significance of paradoxical breathing and mediastinal flap, and how these hazards may be minimized to some extent by pleural adhesions and a relatively fixed mediastinum. Similar difficulties may arise during thoracoplastic operations where the chest wall is unstable despite an intact pleura, or during the removal of thymic or thyroid tumours from the superior mediastinum.

In addition to the embarrassments of an open pneumothorax, the majority of patients requiring thoracic surgery have considerable respiratory disability whether from excessive secretions, previous collapse therapy, pulmonary congestion, or from pressure caused by a tumour or a collection of fluid or air. The importance of proper preparation is now appreciated, and, helped by physiotherapy, by the appropriate antibiotics to control post-operative infections, and by resuscitation, these patients tolerate severe operations remarkably well.

It is now generally accepted that during thoracic operations assisted or controlled ventilation is necessary to provide efficient respiratory exchange, to stabilize the mediastinum, and to reduce diaphragmatic movements, and so to provide satisfactory conditions for the surgeon. Beecher *et al.*, (1951) have recently shown that, whereas the prone and supine positions are more favourable for the natural excretion of carbon dioxide, manual squeezing of the rebreathing bag is essential when the patient is operated upon in the lateral position. Many anæsthetists prefer assisted respiration, but it often appears to me that when a rather inexperienced anæsthetist uses this type of ventilation for thoracic surgery, there is still considerable mediastinal swing which must interfere with venous inflow and cardiac output and have a cumulatively ill-effect on the general condition. Squeezing the re-breathing bag is a helpful guide to the degree of reflex suppression and by the majority of anæsthetists in this country is preferred to mechanical devices for rhythmical inflation of the lungs. I have seen Crafoord's spiropulsator in action on several occasions and it appeared to me to be highly efficient. Its chief drawback lies possibly in its complexity, but a simpler machine, possibly on the Mautz (1941) principle, or the electrically controlled Wolfe-Rand (1950) machine, might be invaluable. Continuous positive pressure anæsthesia is thought to be harmful. With its continuous use there is grave risk of dissemination of sputum into the peripheral bronchioles and of severe circulatory depression resulting from raised venous pressure and lowered cardiac output (Watrous, Davis and Anderson, 1951).

Anæsthetic Technique for Thoracic Surgery

The choice of drugs is to-day largely limited by the use of diathermy, but there are still many clinics where nitrous oxide-oxygen-ether or cyclopropane are used regularly. The introduction of curare, however, has revolutionized anæsthetic methods and we are now able to provide light anæsthesia, with high concentrations of oxygen, with muscular relaxation, and with suppression of reflex responses, without the risk of explosion.

As a general rule anæsthesia is induced by the injection of thiopentone plus a muscle relaxant: the lungs are at once inflated with oxygen and a cuffed endotracheal tube is passed. Anæsthesia is maintained by a closed circuit containing a nitrous oxide-oxygen mixture of at least 30% oxygen. As operation continues, further injections from time to time may be necessary to keep the patient asleep and immobile, and to control respiration. There is no doubt that the care of these patients is very much simpler for all concerned if they are awake and co-operative as soon as the operation is over. With this object in view it is obviously necessary to cut down subsequent doses of barbiturate to a minimum. Indications for further injections of barbiturate include a quickening pulse-rate and rising blood pressure when unrelated to operative interference, and slight movements of the fingers. On the other hand the patient with returning reflexes and increased resistance in the

rebreathing bag (in the absence of secretions), or one who is trying to breathe spontaneously when this is undesirable, needs more relaxant.

Many anæsthetists prefer to use a specific analgesic drug such as pethidine rather than to risk the depressant effects of thiopentone (Mushin and Rendell-Baker, 1950). Anæsthesia is induced with thiopentone and a muscle relaxant, and the patient is intubated and anæsthesia is continued with nitrous oxide-oxygen, 25 to 50 mg. of pethidine being injected intravenously as soon as the patient is in position on the table. Additional doses of 25 mg. of pethidine with or without relaxant are injected as required, which is usually at about half-hourly intervals. Should the operation be prolonged, the time interval between the subsequent doses of pethidine is lengthened to avoid a cumulative effect.

These techniques must of course be modified for patients suffering from *myasthenia gravis*. They do not tolerate curare and are probably better anæsthetized with cyclopropane or with nitrous oxide-oxygen-ether.

Before the pleural cavity is closed the lungs must be fully expanded by gentle inflation, secretions having first been aspirated. It is unwise to apply continuous positive pressure to a lobe or lung which is disinclined to expand; it is preferable to rely on post-operative bronchoscopy and aspiration of air from the pleura checked by X-ray examination. Any risk of tension pneumothorax must be avoided by checking intrapleural pressures or by the insertion of a drainage tube connected to an under-water seal. At the end of thoracic operations atropine and Prostigmin are always given to patients who have had relaxant drugs. An X-ray picture must be taken immediately if both pleural cavities have been opened so that a pneumothorax or collapse may be detected and dealt with at once.

Resuscitation

It is the anæsthetist's responsibility to combat shock and to supervise operative and post-operative resuscitation. As a routine measure an intravenous drip is always started at the beginning of the operation and blood is replaced as it is lost. Simultaneous transfusion into two veins may, on occasion, be needed. I think it is preferable to use a vein on the back of the hand or forearm; this enables the anæsthetist personally to control the rate of transfusion. Blood-drips into the arm, especially the upper arm, seem to run more smoothly than those in the leg, and I have the impression that fewer patients develop thrombophlebitis after them than with saphenous vein transfusions. Intravenous infusions must be given cautiously to patients with cardiac disease or to those with marked venous congestion as a consequence of thoracic injury.

"Wet Lung"

Although the technique I have described will suffice for the majority of patients, there are many others requiring lung resections who need better protection than is possible with a head-down tilt and intermittent suction. These include patients suffering from pulmonary sepsis, whether as a result of bronchiectasis, suppurative pneumonitis, lung abscess, the destroyed lung associated with tuberculosis, or chronic empyema complicated by bronchopleural fistula. Somewhat similar difficulties may arise in the anæsthetizing of patients with large cysts, the contents of which may be emptied into the bronchial tree. Occasionally a giant cyst has a one-way valvular mechanism in the communicating bronchus, in which case inflating the lung causes progressive inflation of the cyst. There is no doubt that the pre-operative preparation of these patients is better than in the early days of thoracic surgery; but occasionally the mobilization of such a lobe or lung may precipitate alarming quantities of pus or blood or both, and protection against such a contingency is of vital importance.

At the present time opinion is divided as to the best methods of preventing the dissemination of secretions; should we adopt some special position on the operating table, occlude the draining bronchus, or use one-lung anæsthesia?

Many positions have been suggested; but, in principle, it is a question of whether one prefers free drainage of secretions or retention of secretions until the bronchus is clamped. Because of the difficulties of operating in the sitting position the prone position is used more often. The prone position advocated by Dr. Parry Brown (1948) encourages free drainage of secretions, but when the Overholt-Langer position (Overholt and Langer, 1949) is used secretions are retained until such time as the bronchus is divided. These positions are particularly useful for children too small to take a blocker, or for upper lobectomies. Many surgeons, however, prefer the better access to the front of the hilum obtained by the standard lateral thoracotomy incision.

The alternative method of bronchial occlusion is satisfactory for patient, surgeon and anæsthetist. There is no spill of secretions, and the lobe or lung to be resected is collapsed and is immobile. There are two types of bronchial blocker in general use. Dr. Magill's blocker is small enough to be used in older children, or to occlude an upper lobe bronchus; whereas the Thompson blocker can only be passed through the 11 mm. bronchoscope, but because it is covered by a nylon mesh bag, it stays more securely in position. Total left bronchial occlusion is a comparatively easy manœuvre, but there is more difficulty on the right side especially where the eparterial bronchus is high in relationship to

the main carina, in which case endobronchial intubation may give better protection. I am convinced that although it is not a suitable method for the inexperienced, the use of a bronchial blocker has enabled us to operate on many patients who would otherwise have been too "wet" to deal with safely. Frequently the patient with most sputum also has a lung which is completely stuck to the chest wall; if one is able to provide a perfectly uncontaminated airway one can always combat shock by adequate blood transfusion.

The larger size Carlens tube may be useful in patients with bilateral segmental disease where the site of the disease makes selective occlusion impossible.

Occasionally one is called upon to anæsthetize babies who require *pneumonectomy for suppurative lesions*. We have had three such cases this year. The anæsthetic technique was similar to that used for older children, relying upon posture and repeated suction to preserve a clear airway. Fortunately in each case it was possible to clamp the bronchus within four minutes of opening the pleura, and all the babies made a good recovery. One child developed severe tracheobronchitis the day after operation but the stridor rapidly diminished when the child was placed in a steam tent.

Bronchoscopy at the conclusion of lung resections is always desirable. Nevertheless, it may carry a definite risk in patients with circulatory depression and then one must decide whether shock is the result of anoxia from an obstructed airway, or a consequence of operative trauma and insufficient blood transfusion. In the former case bronchoscopy is indicated, in the latter it is wiser to rely upon oxygen therapy and rapid transfusion until such time as recovery takes place.

Excessive secretion is not a feature of extra-pulmonary tumours apart from those associated with the thymus; but some of these patients have suffocative symptoms from mediastinal compression and it is occasionally advisable to intubate them using local anæsthesia.

Local anæsthesia still has a place in thoracic surgery and in many clinics is the technique of choice for the Sembs type of thoracoplasty. Xylocaine is becoming increasingly popular on account of its efficient and prolonged action. Local anæsthesia is also best when draining an empyema or lung abscess with the patient propped in a sitting position. I have no personal experience of hypotensive drugs in thoracic surgery.

Cardiac Surgery

With the rapidly increasing scope of cardiac surgery, the management of anæsthesia for these patients has assumed great importance. For present purposes the patients with cardiac disease most likely to benefit from surgery are those suffering from mitral stenosis, constrictive pericarditis or congenital heart lesions including patent ductus arteriosus, pulmonary stenosis and coarctation of the aorta. A smaller number of patients with cardiac ischæmia and aneurysms of the great vessels may also be improved by surgery. Anæsthesia may be relatively simple in those patients whose cardiac reserve is good, i.e. the majority of patients with non-infected patent ductus and the younger patients with coarctation; but the majority are poor risks; some are desperate. The complications of anæsthesia are largely the results of anoxia; if this is avoided it is often surprising how well these patients tolerate anæsthesia and operation. For example—spinal anæsthesia has been used successfully for patients *in right heart failure*, in whom it was proposed to ligate the inferior vena cava. As a result of vaso-dilatation and diminution in the return flow to the right heart and so to the lungs, the patient's condition often improved sufficiently for him to lie flat and sleep comfortably throughout the operation.

Present experience with *mitral stenosis* indicates that the results of valvulotomy are good in those patients whose symptoms are predominantly those of pulmonary congestion or of hypertension, i.e. dyspnœa and cough on exertion, paroxysmal dyspnœa, pulmonary œdema or repeated hæmoptysis, and in those patients whose hearts are small or not greatly enlarged. Auricular fibrillation is not a contra-indication to operation. The few patients with large hearts upon whom we have operated have stood operation and anæsthesia reasonably well, but the final result has sometimes been disappointing. It is too early as yet properly to assess the ultimate result of these operations, and, considering the poor prognosis in this type of patient, a high mortality may not necessarily exclude them. As an emergency measure it is occasionally necessary to operate upon patients having frequent and alarming attacks of *pulmonary œdema*. One of our patients developed such a condition during cardiac catheterization and had a successful valvulotomy performed albeit with very congested lungs. Apart from causing a little anxiety in the next two days, she made an excellent recovery.

Where there is actual decompensation, cardiac function may be improved before operation by rest in bed and by the use of digitalis. Repeated aspirations may be required to relieve ascitic and pleural effusions, and mercurial diuretics, given two days before operation, are advisable for those patients with mitral stenosis whose lungs are congested. Patients with pulmonary stenosis commonly have a respiratory infection with excessive sputum. This should be treated with penicillin.

As well as by the general improvements in intrathoracic technique and anæsthesia, there is reason to believe the dangers and difficulties of cardiac surgery have been reduced by the use of procaine and other drugs, such as quinidine, to diminish the sensitivity and irritability of the heart, and by the local injection of anæsthetic solutions into the nerve plexuses, in the pericardium and myocardium. The value of procaine is, however, debatable.

...arrhythmias occurring during anæsthesia may be of reflex origin or due to chemical changes in the blood stream. In this type of surgery they are commonly the result of direct stimulation and manipulation of the pericardium and heart itself, particularly of those manipulations which dislocate the heart from its normal position. It is possible that an abnormal heart may be more sensitive to unusual stimuli, but as a rule these irregularities stop when the heart is left alone.

Prophylactic measures to protect the heart before operation include the restriction of salt and fluids, and the administration of quinidine, starting twenty-four hours before operation and continuing for two weeks unless there are obvious contra-indications. During operation procaine is given intravenously and as a local injection. Its action, like that of quinidine, prolongs the refractory period of the auricle and reduces irritability of the myocardium, thus raising the threshold of the heart against the production of extrasystoles and fibrillation. For an adult a dosage of 1,000 mg. each hour is generally satisfactory but must be given in only a small quantity of fluid; for this we make up a fresh solution of 0·6% in 5% glucose, a 0·2% solution being used for children.

An anæsthetic technique similar to that already described for thoracic operations in general is equally useful for cardiac surgery, viz. induction with intravenous thiopentone and a muscle relaxant, plus endotracheal oxygen or nitrous oxide-oxygen, using controlled ventilation. Controlled ventilation is practically indispensable during vascular anastomosis. A semi-sitting posture may be necessary when operating on patients with mitral stenosis and severe orthopnœa. Many of these patients have turgid lungs which are difficult to inflate and every opportunity is taken to re-expand gently any partially collapsed lung. The need for supplementary injections of barbiturate is reduced to a minimum when using procaine, and smooth anæsthesia is also facilitated by its broncho-dilating action.

A procaine drip is begun immediately after the induction and the intubation—a double drip technique being used so that blood can also be given if needed. The drip is continued until all manipulations to the heart and great vessels are completed. Amethocaine 0·25% to 0·5% solution is injected into the pericardial sac. It has been suggested that the injection of procaine into the pericardial sac may act as an irritant and increase the incidence of post-operative effusion, but probably manipulation alone could account for such a reaction.

Circulatory depression has followed large doses of procaine and dramatic falls in blood pressure are occasionally seen during mitral valvulotomy. It is not always clear that this is in any way connected with either the procaine or the actual surgical manipulation. We have been afraid, however, of hypotension and its deleterious effects in these patients on the coronary circulation and have tried to raise the pressure by giving small doses of Methedrine intravenously. Despite the suggestion that diseased heart muscle is more sensitive to procaine which may be a myocardial depressant, we are under the impression that since we have used it the heart's action has been smoother and there have been fewer alarming arrhythmias. Although it is customary to make electrocardiographic tracings during cardiac operations, the anæsthetist can gain valuable information as to the strength and quality of its action by observing the heart directly.

Of the complications following mitral valvulotomy, two are worth recording.

Two patients complained bitterly a few hours after operation of pain in one leg. In neither case were the femoral or peripheral pulses palpable and the affected limbs were cold and mottled in appearance. In both cases a 0·4% procaine drip was begun slowly, and in both after a few minutes the femoral pulse returned accompanied by a rapid improvement in the appearance of the limb. In one patient the symptoms recurred during the night and it was found that the procaine drip had stopped; rapid improvement followed its re-establishment; and recovery in both the patients was satisfactory; one can only suppose that small emboli were associated with spasm of the arteries.

Of congenital heart lesions, *pulmonary stenosis* requires special mention. Some patients are mere infants but the children have an average age of about 6. They frequently suffer from respiratory infection which must be improved before operation. There is ample time to get to know these children, who are often spoilt and cross, and to assess their reaction to anæsthesia, as repeated anæsthetics may be necessary for investigations prior to the main operation. Comparatively large doses of morphia or barbiturate are given as premedication to reduce the metabolic rate (and consequently the oxygen consumption) in these children already severely handicapped by inadequate pulmonary flow. For a similar reason the child should be kept cool during the operation, if necessary on a chilled water bed. Cyclopropane or cyclopropane followed by ether-oxygen are sometimes preferred as anæsthetic agents for these children, and any condition which decreases, even momentarily, the oxygen supply to the heart and brain must be avoided. I prefer to use the largest size of plain endotracheal tube which can be passed quickly and gently, and to inflate the lungs with oxygen immediately after intubation, controlling or assisting respiration as required. A 0·2% procaine drip is used. The heart must be watched carefully throughout operation to assess the rate and quality of its action; two signs of grave significance are bradycardia and a visibly weakened beat. Prompt action in inflating the lungs with 100% oxygen and injecting atropine intravenously may improve matters; but if response to this is poor, other measures must not be delayed.

Cardiac Resuscitation

During intrathoracic and particularly cardiac surgery, when the heart is constantly in view, we are in a good position to deal promptly with an emergency. It is probably impossible to resuscitate patients with a dilated and hypertrophic heart or with severe coronary artery disease, or those patients who have extensive pulmonary fibrosis and a vital capacity so low as to be scarcely compatible with life. There is a good chance of success with other patients if treatment is begun promptly and the blood volume be adequate (Beck and Rand, 1949).

The first principle is to inflate the lungs with 100% oxygen through an endotracheal tube and to circulate this oxygen to the brain by cardiac massage; circulation to the brain must be restored within five minutes of its cessation. Whilst this treatment is proceeding it is possible to check by electrocardiograph whether the heart is in ventricular asystole or in ventricular fibrillation. If it is in asystole, cardiac massage alone is usually sufficient, but should restoration of the heartbeat be slow, the injection of 0·5 c.c. of 1 : 1,000 adrenaline into the right ventricle is effective in many cases. For ventricular fibrillation 5 c.c. of 1% procaine are injected into the right ventricle and the same solution applied to the surface of the heart, which is then defibrillated by electric shock. When all fibrillary movements have stopped and the heart is in asystole it is massaged and adrenaline injected.

Abstract.—The present scope of thoracic surgery and the part played by the anæsthetist in special investigations, preparation of patients and assessment of cardiac and respiratory functions before major surgery are discussed.

Satisfactory anæsthesia for thoracic surgery is dependent on a full appreciation of its special problems and the application of suitable methods. The hazards of an open pneumothorax are counteracted by the use of assisted or controlled respiration.

Anæsthetic methods in general use are elaborated, emphasizing the use of a non-explosive technique with nitrous oxide-oxygen, muscle relaxant and supplemented by barbiturate or a specific analgesic drug. Restoration of normal respiratory physiology, rapid recovery, and adequate resuscitation are important factors in reducing post-operative complications.

Dissemination of sputum in patients with excessive secretions during operation is prevented by posture or bronchial occlusion; and the value of post-operative bronchoscopic aspiration after lung resection and immediate post-operative X-ray examination is stressed.

The prophylactic use of procaine and other drugs to diminish sensitivity and irritability of the heart appears to be of value. The management of anæsthesia during cardiac operations is outlined with particular reference to mitral and pulmonary stenosis. Some complications following cardiac surgery are discussed.

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Section of Physical Medicine

President—H. F. TURNEY, D.M., M.R.C.P., M.R.C.S.

[*November* 14, 1951]

Ankylosing Spondylitis

PRESIDENT'S ADDRESS

By H. F. TURNEY, D.M., M.R.C.P., M.R.C.S.

ANKYLOSING SPONDYLITIS is no new disease, but it is only relatively recently that it has been isolated and recognized as a definite clinical entity. Its history dates back to very early times as undoubted examples have been found in the skeletons of Egyptian mummies. The first accurate post-mortem description seems to be that by Connor in 1691 and has been quoted by Buckley and others. Connor's description of the calcification of the intervertebral ligaments leaving the intervertebral discs intact and of the ankylosis of the intervertebral and costovertebral joints allows no room to doubt that he was indeed describing the bamboo spine of ankylosing spondylitis. Clinically no attempt was made to differentiate ankylosing spondylitis from the general classification of spondylitis deformans until the eighteen-nineties when the first real advance was made. This was associated with the well-known names of Bechterew and Marie and Strümpell. Bechterew drew special attention to advanced kyphosis, muscle wasting and signs of nerve root involvement. When one studies the different textbook descriptions of Bechterew's syndrome and even more so the accounts of cases with this label shown at medical meetings it is quite clear that there have been very wide differences of opinion as to what Bechterew's syndrome really is. When in addition we take into account the fact that of Bechterew's original cases two were in women in whom the disease started in the sixth decade of life it becomes reasonably certain that Bechterew failed to differentiate any specific syndrome and that his cases were a mixture of different pathologies, though no doubt examples of true ankylosing spondylitis were included in his series.

Marie and Strümpell on the other hand undoubtedly did describe those advanced cases of ankylosing spondylitis in which the hips and occasionally the shoulders become fixed although they did not connect them with those less severe cases in which this extension does not occur.

We no longer subdivide the disease into the types of Bechterew and Marie-Strümpell. There is a plethora of names: *spondylose rhizomélique*, spondylitis ankylopoietica and spondylitis adolescens, to give but a few. It is to be hoped that the term "ankylosing spondylitis" will now become universal.

It was not till the nineteen-thirties that our present diagnostic criteria, both clinical and radiological, were generally accepted. We now regard the condition of the sacro-iliac joints as shown in X-rays as of prime importance in diagnosis. In 1932 Gilbert Scott pointed out (1942) that the sacro-iliac joints were the earliest to be involved (he, in fact, regarded infection here as the cause of the disease) and claimed that a firm diagnosis of ankylosing spondylitis could be made on the X-ray picture of the sacro-iliac joints before any other part of the spine showed signs of involvement.

INCIDENCE

Ankylosing spondylitis is primarily a disease of youth. The vast majority of its victims are men, young men in the prime of life. Most published series agree in showing that 90% or more are males and that in the majority the disease first shows itself in the twenties, while at least 90% originate between the ages of 20 and 40. A number of cases start in the teens, though I have not heard of any case starting before the age of puberty, and a few in the older age groups. It is probable that at least some of the cases which appear to start in advanced age are in reality merely cases of missed diagnosis or recrudescence of earlier disease. The early symptoms of ankylosing spondylitis may be so mild that medical advice may not be sought or the diagnosis may not be made until the condition is far

advanced. As an instance of this I once saw an elderly labourer who came to hospital for persistent pain following a minor injury. On examination, his whole spine, with the exception of the cervical region, which showed some impaired movement, was rigid and the X-rays were characteristic of ankylosing spondylitis. He at first denied that he had had any rheumatic troubles or any affection of the spine, but on closer questioning he remembered that as a young man he had suffered fairly severely from "muscular rheumatism" over a period of years, but it had never stopped him working and ultimately the pains passed off and although he was aware of the stiffness of his back he had continued doing heavy manual labour until his recent accident. So although we know of no reason why the disease should not start in the later years of life such cases are unusual and the possibility of delayed diagnosis rather than delayed onset should be borne in mind.

It has been stated that ankylosing spondylitis is particularly prone to attack athletes, more especially swimmers, but I have found no evidence of this though naturally with such an age and sex incidence a fair proportion of athletes is bound to be included in any series. I think the idea has arisen as, in this country at least, the average young man, if asked if he is fond of sport, feels it almost a point of honour to answer that he is, even if his enthusiasm does not extend beyond that of the spectator. There is certainly no evidence on which one can suspect athletics as being a causative factor.

Clinical Course

The first symptom of the disease is usually an aching in the lumbar region, hips and thighs, but at times the pains are felt elsewhere and so may be misleading. At first the aches tend to be intermittent, but later become more persistent. It has frequently been noticed that they are worse at night. While this is not invariably so this nocturnal exacerbation is sufficiently frequent and sufficiently marked to make it an important diagnostic factor even if one makes allowance for the fact that discomforts always tend to loom more largely in the small hours. This phase may last for many months before any restriction of the spinal movements can be demonstrated. The vague and intermittent nature of the symptoms combined with the lack of physical signs unfortunately often results in the true diagnosis being missed and cases are too often labelled as "growing pains" in the younger and "fibrositis" in the older patients. It cannot, however, be too strongly emphasized that ankylosing spondylitis is one of those diseases in which early diagnosis is of the utmost importance, as early treatment can make all the difference to the future of the patient.

It is here that the discovery of the early involvement of the sacro-iliac joints is seen at its true value, because even in these early cases the sacro-iliac joints almost invariably show definite radiological changes. Personally I have never seen a case in which such changes could not be demonstrated. It is true that various observers have described undoubted cases of ankylosing spondylitis in which the X-rays of these joints appeared normal, but they must be very rare and for practical purposes normal sacro-iliac joints may be taken to rule out ankylosing spondylitis. On the other hand it is possible to err in the opposite direction. The earliest pathological changes in any condition are likely to be indefinite and nowhere is this more apparent than in a radiograph. Scott, who was an enthusiast for early diagnosis, collected a series of 500 cases of ankylosing spondylitis largely by taking routine radiographs of the sacro-iliac joints of all young people who presented with rheumatic symptoms. In this series nearly 30% were women. This is a far higher proportion of women than the usual experience and it seems to me most probable that here enthusiasm over-reached itself and that minor varieties of the normal were regarded as early stages of disease. It may be that this is an unduly cynical explanation of the high proportion of women in this series and that the true solution is that in women a high proportion of abortive cases occur which never emerge from the subclinical stage. Although I would agree that in general the disease runs a more benign course in women than in men and that in women the severest forms of deformity and disability are less likely to occur, I can find no evidence for such a proportion of abortive types as would be necessary to explain the discrepancy and I still feel that the diagnosis was at fault.

If no treatment is given the pains persist and movement of the spine becomes increasingly restricted. The rigidity starts in the lumbar region and spreads upwards, the cervical spine becoming involved last and often here a small range of movement remains after the rest of the spine is completely ankylosed. In the dorsal region the costovertebral joints become involved resulting in fixation of the thoracic cage and defective or absent respiratory movement. The lumbar curve becomes flattened or even reversed and concurrently a kyphosis develops and may increase until the spine is bent through a full right angle. This, together with the rigidity of the neck, may prevent the unfortunate sufferer from seeing anything more than a foot or two in front of his toes when standing. The characteristic posture is thus developed with the body thrust forwards and the head tilted upwards as far as the stiffness of the neck will allow. The forehead becomes deeply furrowed owing to the upturning of the eyes in an endeavour to see forwards when walking. In about 20% of cases one or both hips also become affected and finally ankylosed. In a smaller proportion the shoulders also become fixed and in relatively rare cases the more peripheral joints too become involved leaving the patient in a most pitiable condition with all his joints immovable.

In the great majority of cases the disease runs true to type, starting at the sacro-iliac joints and spreading as a regular outward-flowing tide first up the spine and then out to the limbs, but occasionally we meet cases in which this orderly peripheral spread is replaced by a more erratic course. I once saw a case in whom the first joint signs occurred in the knees. The patient admitted that he had been conscious for some time of a slight stiffness in the back, but he was quite definite that he had had no pain and had never sought medical advice till his knees gave trouble. In spite of X-ray therapy the disease progressed and in the course of some five or six years he has been left completely crippled. Besides complete rigidity of the spine he has ankylosis of the knees, ankles, wrists and one shoulder, the intervening joints and the hands and feet being unaffected. This mode of spread is very unusual and may at first be misleading.

Although the order of involvement of joints is usually a regular one the rate and mode of progress is very variable. Some cases have an acute onset with severe pain and fever which compels them to take to their beds at an early stage, but the majority are able to keep about. Some cases run a steady downhill course to become helpless invalids within a few years, while others smoulder on for years with relatively little incapacity. Sometimes there are periods of activity followed by periods of quiescence when the patient may feel perfectly well, though possibly inconvenienced by the damage already caused. Again the disease may burn itself out at almost any stage between the extremes of simple ankylosis of the sacro-iliac joints alone and complete fixation of most of the joints of the body. Approximately one-third of cases remain mild, resulting in only limited restriction of spinal movement, one-third are of moderate severity with ankylosis of the whole spine but without serious deformity, and one-third are severe with gross kyphosis and/or involvement of the peripheral joints. It is, however, never possible to be sure that a permanent arrest has been achieved as a recrudescence may occur even after several years of quiescence.

As the disease progresses there is marked muscular wasting and an advanced case may be quite severely emaciated. Some writers have been so impressed with this muscular wasting that they have postulated cord or nerve involvement to account for it. I do not think that there is any need for this as a widespread and debilitating arthritis is quite enough to produce it. Objective signs of nerve pressure are in fact unusual although symptoms suggestive of nerve irritation such as girdle pains and sciatica are quite common.

A raised erythrocyte sedimentation rate is an almost invariable accompaniment of the active phase of the disease, though it may drop to normal during quiescent periods. This may be a valuable aid in confirming the diagnosis. However, it is not nearly so reliable as the X-ray changes and it is on the radiological picture that one depends to clinch the diagnosis after suspicions are aroused by the clinical examination. The earliest X-ray signs occur in the sacro-iliac joints. These consist of a widening of the joint space and a woolly appearance of its outline which should normally be clearly defined. There is some rarefaction of the underlying bone. It is at this stage, when the rest of the spine is unaffected, that one would like to make the diagnosis, but usually this stage is over by the time the patient is first seen. In the next stage sclerosis replaces the rarefied bone and the calcification finally spreads over the whole joint resulting in a solid bony ankylosis, in fact it may be impossible to detect the original site of the joints. The same process affects the intervertebral facets and, in the dorsal region, the costovertebral articulations and they become solidly fused.

The orthodox description is that calcification also spreads throughout the intervertebral ligaments leaving the intervertebral discs intact and without reducing the intervertebral spaces, thus producing the classical bamboo spine when seen in the dried specimen. However, at the 1951 Rheumatic Congress at Barcelona Professor van Swaay read a paper which, if confirmed, will lead us to alter our views. As the result of post-mortem examinations on three cases he found that so far as the sacro-iliac and intervertebral joints are concerned the initial process is a proliferation of cartilage cells which extend across the joint space and invade the opposing cartilage. This cartilaginous ankylosis subsequently becomes calcified to produce the well-known end-result. This is a completely new conception and one must await its confirmation. More surprising still van Swaay found that the intervertebral ligaments were quite normal, the calcification between the vertebral bodies occurring in the fibrous rim of the intervertebral disc itself.

Whatever may be the mode of production the result in a radiograph is to show a thin line of calcification joining the vertebral bodies at their periphery and a heavy line of shadow cast by the fused apophyseal joints—sometimes called the "tram line" effect. In contrast with this excessive calcification the vertebral bodies show a marked osteoporosis.

Complications

The one complication specific to ankylosing spondylitis is iritis. It occurs frequently. About 20% of patients suffer from it during the course of the disease and in some cases there are multiple attacks. As recorded by Tegner and his colleagues (Birkbeck *et al.*, 1951) it may be the symptom which first brings the patient under medical supervision. In all Tegner's cases there were well-marked sacro-iliac changes showing that the disease was of some duration.

An anæmia of secondary, microcytic type, is of frequent occurrence and may have a very adverse effect on the patient's progress, so a close watch on the blood picture is called for. The anæmia usually responds well to iron therapy.

The only other complications likely to arise during the course of ankylosing spondylitis are respiratory complaints, and their gravity is greatly increased by the fixation of the thoracic cage. Bronchitis, pneumonia and pulmonary tuberculosis are all liable to occur and, before the introduction of our modern range of antibiotics, formed between them the chief reason why so few spondylitics achieved the allotted span of life. With modern treatment this source of danger has been greatly reduced.

Pregnancy is unusual in this condition, partly because women form so small a proportion of its victims, but possibly also because of a reduction in fertility in its sufferers. When it does occur it usually presents no special difficulty. Even with a completely rigid spine parturition is easily accomplished. The one thing which may cause difficulty is fixation of the hips and this may render normal childbirth impossible and make Cæsarean section imperative.

Cause

The cause of the disease we do not know. Attempts have been made to take cultures from the sacro-iliac joints. At operations in the acute phase the joints are found to be filled with soft amorphous material, but cultures from this material have failed to produce any useful result, usually being contaminated.

The tubercle bacillus has been suggested as a possible culprit, but no convincing evidence of this has yet been produced. Sufferers from ankylosing spondylitis tend to show a high proportion of positive reactions to the tuberculin test and also a higher incidence of pulmonary tuberculosis, but the tuberculin test is a very shaky foundation to build on and when one considers the debilitated state of the average spondylitic and the severe impairment of his respiratory movements it is not surprising that he is liable to fall a victim to any superadded respiratory infection. Furthermore bony tuberculosis is most common in children in whom ankylosing spondylitis does not occur and the enormous reduction in surgical tuberculosis in recent years has not been accompanied by any reduction in spondylitis which, on the contrary, appears to be more prevalent. That ankylosing spondylitis is a form of tuberculosis thus appears highly unlikely.

The gonococcus has also been suggested as a possible infecting agent, but although the end-result of gonococcal arthritis can be very similar to that in spondylitis there is no other evidence to support the suggestion, and I think it can safely be discarded although I believe in France they take a more serious view of its possibilities.

Various biochemical investigations (Desmarais *et al.*, 1948; Desmarais, 1949) have been carried out in an endeavour to elucidate the cause of the disease, but so far they have resulted in no progress. In view of the predominantly male incidence the excretion of 17-ketosteroids has been estimated in several series of cases. In some instances the output has been found to be high, but in general it is within normal limits and certainly gives us no help either in the diagnosis or the understanding of the disease. The same can be said of the phosphatase content, both acid and alkaline, of the blood. At the moment, in fact, we are completely in the dark on the question of causation.

In America ankylosing spondylitis has come to be regarded as a form of rheumatoid arthritis under the name of rheumatoid spondylitis (Dunham, C. L. and Kautz, F. G., 1941). This idea has, I think, arisen because some cases of ankylosing spondylitis develop in the peripheral joints, notably of the hands, an arthritis indistinguishable from rheumatoid arthritis. As I have already indicated, in this country we prefer, in the present state of our knowledge, to regard the two diseases as separate entities, partly because the instances when the two conditions appear to occur simultaneously are so uncommon that it is impossible to regard them as in any way typical of either disease, but chiefly because the whole picture of the two diseases is so entirely different. There is the sex incidence—two-thirds female in rheumatoid arthritis, and 90% male in ankylosing spondylitis; the mode of spread—rheumatoid arthritis starting at the periphery and spreading to the bigger joints, spondylitis starting at the centre at the sacro-iliac joints and spreading up the spine and at times to the bigger peripheral joints, but rarely affecting the hands and feet. When we consider the detail of the arthritis we find that the chief features in spondylitis are calcification of ligaments and bony ankylosis. Although around affected joints there is some rarefaction of the bones, there is no general osteoporosis. The reverse is true of rheumatoid arthritis where there is a general osteoporosis and where calcification is notably absent. Again the reaction to X-ray therapy and gold is diametrically opposite. X-rays are of great value in spondylitis and gold in rheumatoid arthritis; transpose the treatments and they become valueless. Kersley and his colleagues at Bath have consistently failed to find in muscle biopsies of spondylitics those foci of round-celled infiltration which are so characteristic of rheumatoid and finally van Swaay states that he found no evidence of rheumatoid arthritis in his cases and that the synovial membranes were unaffected.

With such an array of evidence against it I find it difficult to understand the American point of view.

Treatment

The one form of treatment which has a definite curative value is radiotherapy and the earlier radiotherapy is started the greater is the prospect of arresting the disease. Gilbert Scott was among the earliest to advocate the use of X-rays and he was most insistent on the importance of early diagnosis, claiming complete arrest of the disease in something approaching 100% of cases when treatment was given in the "pre-spondylitic" phase when only the sacro-iliac joints were involved.

I cannot take quite such an optimistic view as I have certainly seen many cases in which the disease continued to progress in spite of radiotherapy. This discrepancy may be partly due to the fact that most of my patients have been past the pre-spondylitic phase when first seen. There is also the difficulty which I have already mentioned of the diagnostic criteria. At the same time it is quite certain that the great majority of patients will be benefited by X-rays and that a good proportion will obtain complete arrest. Naturally in the later stages when extensive calcification has occurred it is useless to expect too much, but it is often surprising how much mobility will return to a joint, which on clinical examination appears completely fixed, following a course of deep X-rays, while relief of pain may be most striking.

Scott used a wide-field technique for administering X-rays which had the advantage of causing little constitutional disturbance, but this has now been generally abandoned in favour of intense irradiation of the whole spine and if necessary of the peripheral joints. Improvement usually starts within the first few weeks but full benefit may not be obtained for a number of months. It is well to warn patients that considerable constitutional upset may occur, as one of my patients, in whom this was omitted, feeling that the treatment was doing him more harm than good absented himself from the remainder of the course after the first few sessions. When seen many months later the disease had made considerable progress and one shoulder had become completely fixed.

Fortunately most of our patients are males in whom there are no vulnerable structures which cannot be protected from the rays, but a considerable problem arises in the case of young women. It is not possible to irradiate the sacro-iliac joints without, to some extent, affecting the ovaries. Obviously sterilization is undesirable and this can usually be avoided by a tangential application of the rays, but even so the ovaries are bound to receive a certain dosage and the danger of causing a mutation of genes arises. This is a danger which is difficult to assess, in fact some may regard it as distinctly nebulous, but at least in theory such a mutation might ultimately result in greater distress than would an immediate sterilization. My own view is that in women of the child-bearing age and especially in young married women it is safer to avoid the region of the ovaries and to content oneself with treating only those regions of the spine which can be irradiated in safety, though in a severe and progressive case it would be quite justifiable to accept the risk and irradiate the sacro-iliac region as well.

Gold has been widely tried and as widely discarded. With its well-known dangers there is no justification for its further use. Of cortisone I have no experience. Good immediate response has been claimed, but I have seen no accounts of long-term treatment. Thus radiotherapy remains our one means of making a direct attack on the disease.

For the general treatment of spondylitis our chief standby is rest—rest combined with graduated exercises. In view of the great tendency to fixation of joints absolute rest is contra-indicated, though in an acute phase it may be that the only thing which gives the patient any comfort is a plaster bed giving complete support and immobility to the spine. The plaster bed may also be essential in the face of a rapidly developing kyphosis. But even in such cases regular movements of the hips and shoulders should be carried out and, even more important, deep breathing exercises for the maintenance of thoracic movement. The plaster bed is not often necessary and usually all that is needed is to provide a firm mattress without sag and to advise sleeping on the back without a pillow, or at most with a very low pillow. This position for sleeping is often difficult to get accustomed to and sedation will be called for at first, but its importance is such that it is well worth putting up with considerable preliminary discomfort until the new habit is formed. Ambulant patients, besides sleeping on the back, should if possible take a midday rest lying flat and should also lie flat at those times when they would normally be relaxing in a chair. I attach the greatest importance to this question of rest. Muscular fatigue sets in very rapidly with these patients and it is then that the body begins to sag and a kyphosis develops. This principle should be continued until the disease is completely quiescent or the spine is so firmly fixed that no further deformity is likely to occur.

Combined with rest graduated exercises should be carried out. All spinal movements should be practised but particularly extension exercises of the kyphosis type for strengthening the spinal muscles. It is often valuable to assist them with spells of mechanical extension with a traction apparatus.

Hip and shoulder exercises are also important. Involvement of these joints can be very insidious and quite a large range of movement may be lost before the trouble is discovered unless joint movement is regularly tested. I have already mentioned breathing exercises. These are important throughout

and particularly so when there is a kyphosis to act as an additional embarrassment of thoracic movement. It is well to remember that although ankylosing spondylitis is not of itself a fatal disease it does carry a considerably increased mortality almost entirely due to chest complications.

Considerable discrimination is necessary in the prescription of exercise. Violent exercises are contra-indicated. Besides being painful I think they may actually hasten any tendency to ankylosis. Generally speaking the patient's feelings are a good guide. If he feels that exercises are stirring up his trouble, it is probable that too much is being attempted.

Should a kyphosis show signs of developing in spite of this type of regime a spinal brace is indicated if the patient is to remain ambulant. A spinal brace, too, is usually desirable for the first months of ambulatory treatment for such cases as have needed a spell of complete rest in a plaster shell. A brace is an uncomfortable apparatus and many patients do not take kindly to it; but it is a mistake to delay its use until the kyphosis has reached serious proportions. A brace is an excellent preventative, but once the deformity has started it may be extremely difficult to prevent its natural tendency to increase by any means short of complete rest. There should be few cases in which this deformity cannot be prevented provided it is taken in time. Unfortunately the same cannot be said for ankylosis which may occur in spite of all our efforts.

Finally surgery can offer relief from the resultant disabilities in a few cases. Fixation of the hips is an extremely crippling defect and some cases have done well after cup arthroplasty. Unfortunately the great tendency to new bone formation militates against the long-term success of the operation. Smith-Petersen has found that "revision", as he terms it, of the operation often has to be carried out, sometimes more than once. This must be a most intimidating prospect—a prospect which only too many of our cases with their debility and muscular wasting are in no form to face. On the other hand youth is usually in their favour and in the occasional selected case the operation can give satisfactory results.

The second operation (Smith-Petersen) is osteotomy of the lumbar spine in which removal of the laminæ and articular facets of the upper lumbar vertebræ allows the upper part of the spine to be angulated backwards and held by plaster in its new position until consolidation is complete. Extremely good results have been reported in cases in which extreme kyphosis and rigidity of the cervical spine result in the line of vision being directed vertically downwards. The tilting back of the upper spine raises the angle of vision towards the horizontal and allows forward vision. I have no personal experience of this operation and one hopes that it will be needed but rarely, because the patients for whom it is suitable represent a major therapeutic defeat, as with early and adequate treatment such extreme deformity should not arise.

Conclusion

Finally to sum up the problem of ankylosing spondylitis: the crux of the whole matter lies in early diagnosis followed by early and efficient treatment. Once the disease has been suspected diagnosis from an X-ray of the sacro-iliac joints is usually easy, but in spite of this, published records show that the average patient has complained of symptoms for many months and even years before the true diagnosis is made. There is no doubt that the earlier deep X-ray therapy is started the greater is the chance that the disease will be arrested before irremediable damage is done. Heald once suggested mass radiography of the sacro-iliac joints in the same way as mass radiography of the chest is so widely practised. Most of us would consider this as too drastic a proposition, but there is certainly a case, as suggested by Scott, for the routine radiography of the sacro-iliac joints in all young people who complain of rheumatic pains for more than a few weeks unless there is a clear alternative diagnosis. If this were done and all positive cases submitted to X-ray therapy at once, although it cannot be claimed that the disease would be eradicated, I believe that this source of crippling and invalidism would be materially reduced, but even so until we have some more reliable method much of the treatment of ankylosing spondylitis will still be thrown on to the Department of Physical Medicine.

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Section of Endocrinology

President—A. W. SPENCE, M.D., F.R.C.P.

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DISCUSSION ON SOME ASPECTS OF RENAL FUNCTION IN ADDISON'S DISEASE AND HYPOPITUITARISM

Dr. A. A. G. Lewis (Department of Medicine, Middlesex Hospital):

The history of the growth of our knowledge of renal function in adrenal deficiency reflects in miniature the recent history of renal physiology. Gaillard in 1914 noted that renal failure and a high blood urea occurred in this condition. Marshall and Davis (1916) showed that injected urea and creatinine were excreted more slowly than normal while Bevier and Shevky (1919) showed that the Addis excretion ratio for urea—what we should now call the urea clearance, measured over an hour—was diminished. In 1933 Loeb *et al.* showed that there was an increased loss of sodium in the urine after adrenalectomy and in 1936 Harrop *et al.* demonstrated the reduced potassium excretion. Both these workers rejected Swingle's suggestion (Swingle *et al.*, 1933) that the urea retention was due to fluid loss, low plasma volume and low blood pressure, because it often occurred at a time when the urine flow was above normal—in Harrop's words, it was not due to a reduction of the water available for urea excretion. Others believed that the retention of urea maintained fluid osmotic pressure after salt loss—a variant of the old French concept of uræmia from lack of salt. This confusion could not be resolved until modern methods of studying renal function could be applied. In 1938 Margitay-Becht and Gömöri, using the creatinine clearance, showed that glomerular filtration was low in adrenal insufficiency, and in 1942 Talbott *et al.* published the first complete study of renal function in Addison's disease, using inulin and diodrast. Glomerular filtration rate, renal blood flow and filtration fraction were all low, and were only partially and temporarily restored by salt, desoxycorticosterone acetate or cortical extracts. These findings were confirmed by Waterhouse and Keutmann (1948), and by Sanderson (1948) in this country. The low urea clearance, of course, results from the low filtration rate. The low renal blood flow and filtration rate are evidently partly the result of the reduced blood pressure, blood volume and cardiac output, but there appear to be unexplained changes in glomerular arteriolar tone as well.

Recent experimental work has centred mainly on the problems of tubular water and electrolyte absorption. In adrenal deficiency the tubules fail to reabsorb sodium normally from the glomerular filtrate, so that if salt is withheld the urine contains a higher concentration than normal. It is not generally realized, however, that the reverse is also true: Willson and Sunderman (1939) found that in dehydration a patient could not concentrate sodium as high as a normal control and salt was retained. In Addison's disease, therefore, the urinary sodium concentration and excretion can only be varied within much narrower limits than normal. Reforzo-Membrives, Power and Kepler (1945) found that the ratio of the urinary concentration of sodium at night to the lowest during the day varied in normals from 5·8 to 12·8, but in Addisonians it lay between 0·9 and 1·3. Harrison and Darrow in 1939 maintained that the primary change is a failure of the renal tubules to maintain the necessary

concentration differences between urine and plasma with respect to certain ions. Studying adrenalectomized dogs, Roemmelt, Sartorius and Pitts (1949) found that these anomalies were not due to inability of the tubules to perform the necessary osmotic work to dilute or concentrate the urine. When hypertonic saline is infused into normal dogs an osmotic diuresis results: the urine flow rises and the sodium is rapidly removed at a concentration closer to the plasma level than before, so that tubular osmotic work approaches zero. In the adrenalectomized animal, the concentration remains well above plasma level and much more osmotic work is done. These workers believe that there is a specific tubular defect imposed by the hormonal imbalance.

Just as the tubules cannot respond to the demands made on them for sodium retention or excretion, they cannot respond to demands for variations in water reabsorption. Urine volume is not reduced to normal levels at night or in dehydration and is not adequately increased in response to a water load. When a normal person drinks a litre of water, blood dilution leads to cessation of the activity of the neurohypophysis, removal of the circulating antidiuretic hormone, decreased tubular water reabsorption and so to a rise in the rate of urine flow. At the same time the urinary chloride concentration and specific gravity fall. Usually the urine flow rises to a peak rate above 10 c.c./minute and, once the diuresis has begun after a delay of about thirty minutes, more than half the water is excreted in the next hour.

In adrenal deficiency this response is reduced or absent, there is less dilution of the urinary chlorides and the water is excreted much more slowly. There has been some confusion about the meaning of the term "delayed diuresis". Obviously the water must be eliminated eventually or water intoxication will occur sooner or later, and the Addisonian passes more urine at night anyway. In this sense the excretion *is* delayed, but we have not seen anything corresponding to the diuretic response, defined above, occurring after a much longer interval than normal.

In panhypopituitarism, all these deficiencies found in Addison's disease also occur, but the position is complicated by the absence of growth hormone. White, Heinbecker and Rolf (1949) have shown that daily injections of growth hormone will double the filtration rate and renal blood-flow of normal dogs and restore these functions after hypophysectomy, though the absence of these effects after adrenalectomy raises the suspicion that some contamination by ACTH may have been partly responsible. Recently Ingbar *et al.* (1950) have shown that large doses of ACTH will increase the filtration rate and renal blood flow of normal men.

Thorn and his group, of which Dr. Slessor was a member, showed in 1950 that the diuretic response could be restored by cortisone. Dr. Chalmers and I working on the Medical Unit at Middlesex Hospital have shown that in hypopituitarism ACTH will restore this response (Chalmers and Lewis, 1951). We have also had good results with cortisone.

Fig. 1 shows the percentage of a litre of ingested water excreted 30 to 90 minutes later by our 6 cases before and after ACTH or cortisone.

Cases 1 and 2 were men with chromophobe adenomas. Case 3 was a very interesting one of hypopituitarism following post-partum hæmorrhage. She retained her body hair and had a Robinson-Kepler test which was just normal, but had very low B.M.R. (— 34%) and great insulin sensitivity. Cases 4 and 5 had classical Simmonds' disease. Patient 5 had cortisone on another occasion. Patient 6 had cortisone.

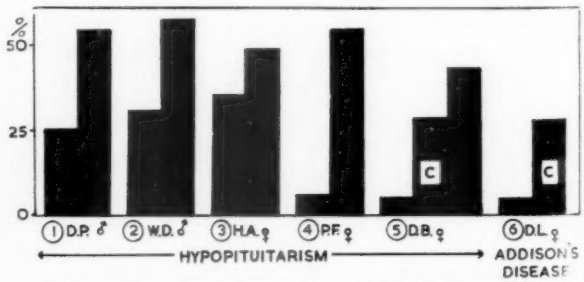

FIG. 1.—Percentage of water load (1,000 ml.) excreted in the period half to one and a half hours after ingestion. Left-hand columns = before ACTH; right-hand columns = after ACTH. C = Cortisone.

Judging by the euphoria and reduced eosinophil count, all the first 5 patients had a satisfactory response to a total of 200–250 mg. ACTH given in six-hourly doses.

Fig 2 shows the actual diuretic responses before and after the course of ACTH, in the most severe case. The Pitressin contamination of Armour ACTH often leads to the retention of a lot of water: some hours after the last injection the patient may begin to pass large volumes of dilute urine and lose weight. This itself shows that the kidney can now excrete water normally, but it is not a diuretic response as we have defined it, so the test is repeated the next day. Two or three days later the response can no longer be obtained. However, much of the subjective improvement seems to last for many months—our patients have staunchly maintained that they have never gone back to their original state. Dr. Dudley Hart (1951) has also reported this after short courses of ACTH in hypopituitarism.

The possible causes that have been suggested for the failure of the diuretic response may be summarized as follows:

(*a*) Delayed absorption of water from the gut.

(*b*) Sodium depletion.

(*c*) Low glomerular filtration rate.

(*d*) Increased activity of the antidiuretic hormone: (i) over-production (faulty osmoreceptors); (ii) delayed destruction; (iii) increased tubular responsiveness.

(*e*) Presence of other antidiuretic substances in the blood.

(*f*) Inherent tubular abnormality.

(*a*) The first can be certainly ruled out clinically: no diuresis occurs after intravenous water, and we have shown that there is a normal plasma dilution when the patients drink a litre.

(*b*) Baldes and Smirk (1934) showed that there was a reduced diuretic response to water in salt-deficient states. However, this cannot be the cause in our cases, for the plasma sodium was not low in our cases of hypopituitarism, and the diuretic response is not restored by large quantities of salt or DOCA.

(*c*) Fig. 3 compares the effects of ACTH on water diuresis and glomerular filtration. It will be seen that there is no relationship between them. In only one case has the filtration rate risen to normal, while in three it has hardly risen at all, yet in only one does the excretion of water fall far short of normal after treatment. (In Case I the urea clearances were measured.)

(*d*) The theory of increased antidiuretic hormone (ADH) activity is a very interesting one. As long ago as 1918 Addis believed that normal renal water excretion depended on a pituitrin-adrenaline equilibrium, and Silvette and Britton later suggested (1938) that it depended on a pituitrin-adrenocortical balance. This hypothesis has been greatly elaborated by Gaunt and his co-workers

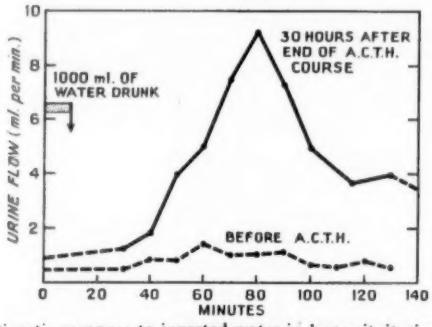

FIG. 2.—Diuretic response to ingested water in hypopituitarism (Case 4).

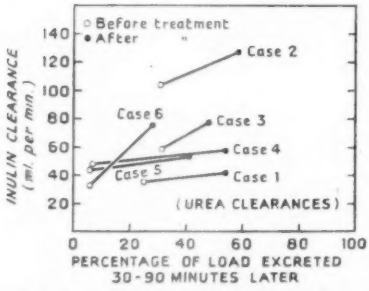

FIG. 3.—Glomerular filtration-rates and diuretic responses in hypopituitarism (Cases 1–5) and Addison's disease (Case 6).

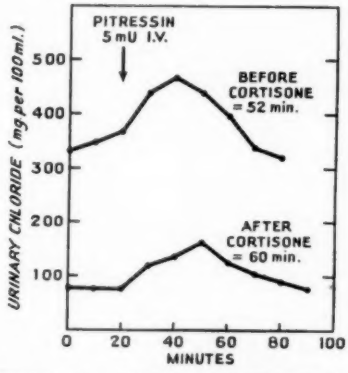

FIG. 4.—Duration of response to intravenous Pitressin in Addison's disease (Case 6).

(Figs. 2, 3 and 4 are reproduced by permission of the *Lancet*.)

(1949). It was believed that ADH reduced tubular sodium and chloride reabsorption but Chalmers, Pawan and I (1951) have shown that this is not true in man, and O'Connor (1948) has done so in the dog. Consequently the overactivity of ADH cannot be blamed for the anomalies of sodium excretion, even if it were responsible for the absence of the water diuresis. If delayed destruction of the hormone or increased tubular responsiveness were the cause of this, we should expect the diuretic response to occur after a longer interval than normal, but to be otherwise much the same with regard to volume and fall of chloride concentration and specific gravity. We have never observed this. Reforzo-Membrives's figures do not show it. Moreover we have tested the responses of our cases to small intravenous doses of Pitressin before and after treatment. Fig. 4 shows the duration of the responses to 5 milli-units in our case of Addison's disease before and after cortisone. We have used the urinary concentration of chloride as an index of the response because of the difficulties of measuring the very small volumes accurately—the latter are, of course, the reciprocal of the former.

Though we have not ruled out the possibility that the osmoreceptors are faulty and that ADH is still produced after normal blood dilution, we believe that the *action* of ADH in these cases is in all respects normal.

(*e*) Dr. Slessor (1951) has published a good deal of work in connexion with this point. I will only refer to it briefly. My criticisms are directed against attaching any significance to the presence of serum antidiuretic substances rather than against any particular experimental results.

Gaunt and his associates (1949) have shown that there is a substance in rat's serum which is antidiuretic on injection into other rats. Lloyd and Lobotsky (1950) showed that human serum contains an antidiuretic substance, the titre sometimes being equivalent to as much as 5 mU. of Pitressin per c.c. when assayed on hydrated rats. They claimed that the titre was increased in Addison's disease. They give few actual figures, however. Fig. 4 showed the response of a case to 5 mU. of intravenous Pitressin. We really cannot believe that *every c.c.* of her blood contained that quantity. When assayed by Lloyd's technique, serum from Case 4 contained none at all, and this was the patient with no diuretic response whatever. On the other hand, serum taken from our first case, just before he drank a litre of water, was strongly antidiuretic, yet he went on to give an almost normal response, after a normal interval, on this occasion. We suggest that no significance can be attached to the presence of this substance.

(*f*) We are therefore left with the conception of renal tubules in adrenal deficiency which are inherently incapable of those exquisitely flexible responses which finally maintain the water balance of the normal organism.

It is possible that the osmoreceptors controlling the release of antidiuretic hormone are similarly defective and we are now working to decide this point. Be that as it may, we are sure that cortisone will largely restore the flexibility of the tubular response to water, and do so quickly. Stimulation of the adrenal cortex to produce steroids of this type is clearly equally effective in hypopituitarism.

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Dr. A. Slessor (Materia Medica Department, The University, Glasgow):

It is my main purpose to present some observations on the antidiuretic (AD) activity of the blood and urine in relation to the problem of faulty water diuresis found in patients with adrenal insufficiency. By doing so I do not imply that other factors are not concerned, such as rate of absorption from the gut and glomerular filtration.

My interest in the phenomenon from the point of view of an antidiuretic factor being involved began in 1946 when we had in the wards two men with hypopituitarism. Each patient presented the typical clinical and biochemical features of chronic lack of the anterior lobe hormones. They differed, however, in one important respect—their excretion of water. One failed to conserve water; the other failed to excrete ingested water promptly. Patient A. L. had developed diabetes insipidus quite suddenly three months before his admission to hospital and fourteen years after his first symptoms of anterior hypopituitarism. The other patient, D. W., who had a similar duration of anterior hypopituitarism failed to have a prompt diuresis when the Kepler water test was applied. In the patient with the diabetes insipidus it was reasonable to assume that neurohypophyseal function had been substantially reduced by an extension of the lesion which had already destroyed the anterior lobe. The other patient presented the expected phenomenon of failure to excrete promptly a large water load—a feature which theoretically could be brought about by an excessive activity of the neurohypophysis. The question was thus posed: did the destruction of the posterior lobe in patient A. L. remove the factor responsible for the absence of water diuresis usually seen in such cases? If this were so it might be possible to demonstrate an increased titre of AD substance in the blood of adrenal deficient patients who showed water retention.

A pilot experiment was thus carried out in collaboration with Dr. J. D. P. Graham. In rabbits undergoing a saline-induced diuresis, plasma from heparinized fasting blood from the hypopituitary patient (D. W.), who showed a positive water test, was markedly antidiuretic. Plasma from the patient with hypopituitarism and diabetes insipidus (A. L.) and from a normal person showed no significant AD activity (Slessor, 1951*a*). In a third case of hypopituitarism, who also showed the phenomenon of temporary water retention, AD activity of the fasting plasma was also demonstrated.

While in America I had the opportunity of making similar observations in patients with Addison's disease (Slessor, 1951*b*). The test animal used was the rat and the method of assay was Birnie's modification (1949) of Burn's method (1931). The test material was serum of fasting blood taken after fourteen hours without food or fluid. 7 Addisonian subjects and 7 normal persons constituted the clinical material.

In Birnie's method the percentage excretion of the water load at 90 minutes was taken as a measure of the antidiuretic activity of the serum injected. For normal subjects the mean value at 90 minutes was 55·0 $\pm$ 1·60; for the patients with Addison's disease 37·03 $\pm$ 5·96; for saline controls 68·79 $\pm$ 2·35. The differences between the means are statistically significant.

It thus seems that there is present in the fasting blood of patients with adrenal insufficiency (both primary and secondary to hypopituitarism) an increased titre of an antidiuretic substance. It seems very probable that this factor plays a part—perhaps an important part—in determining the failure of water diuresis seen in these patients.

Before the method of Birnie *et al.* became available, one had embarked on urinary AD assays. Two observations suggested they might be worth while. First, in patients with adrenal insufficiency the degree of dilution of the plasma electrolytes following the standard dose of water in the Kepler test was of the same order as that obtained in normal persons (Slessor, 1951*b*). When dilution of the plasma electrolytes occurs, according to Verney the posterior lobe ceases to secrete the antidiuretic hormone. In healthy people, diuresis ensues; but in patients with adrenal insufficiency, although dilution of plasma electrolytes of degree equal to normal occurs, no diuresis ensues. Was the failure of prompt diuresis associated with measurable AD activity of the urine passed during the phase of hydræmia? The second observation was this: in most but not in all patients, a late phase of at least partial diuresis did occur after water loading. Was this late phase of diuresis associated with a reduction in AD activity of the urine? The answer to these questions was sought using the method of assay of Ham and Landis (1942). In the 3 patients so investigated AD activity was not found in the urine passed during the late phase of diuresis; while measurable activity was found in the urine passed in the four hours of the water test (Slessor, 1951*b*). Absence of diuresis is thus associated with AD activity in the urine; the later diuresis with no AD activity.

In summary, in the untreated patient with adrenal insufficiency there is an increased titre of AD substance in the fasting blood. A water load while producing a hydræmia fails to induce a coeval diuresis. The urine passed during the phase of hydræmia has a measurable AD activity. The urine passed in the phase of late diuresis contains no AD activity. The conclusion is that some process or processes concerned with water diuresis are slow in adrenal insufficiency; one such process is the removal of an AD substance.

We had assumed from the beginning of the study that the AD substance was of neurohypophyseal origin but the amount found in the blood gave rise to some misgiving. The quantity in serum is of the order of 1 mU. per ml. The equivalent of 2 to 3 units in terms of posterior pituitary extract

would thus be circulating in the blood. This high quantity makes one wary of accepting its posterior pituitary origin without other evidence, but in itself is not a strong negative point. There is the possibility that the AD material is an artefact formed during blood coagulation such as Dicker (1950) found in the serum of rats showing starvation œdema. In our early studies, however, heparinized plasma, not serum, was used, and this was shown to possess AD activity. A more serious criticism comes from Dr. A. A. G. Lewis who has found that the amount of AD substance present in the blood of a patient bears no relation to the degree of impairment of water diuresis existing in that patient. We have not done, as yet, any studies of this kind. There is a distinct variability in the water test, as well as other tests, in some patients with partial hypopituitarism: on some days near normal results are obtained; on others classical absence of diuresis occurs. Perhaps there is a corresponding variability in AD titre of the serum.

If the AD substance is not identical with the antidiuretic hormone there is evidence that the neurohypophysis is concerned in some way with its elaboration. Gaunt *et al.* (1949) have shown that total hypophysectomy abolishes the increased AD activity found in the serum of adrenalectomized rats. Further, patients with anterior hypopituitarism are able to develop diabetes insipidus, and in one such patient whose blood was tested for AD activity, none was found. Thus the indications are strong but not yet conclusive for a posterior pituitary origin for the AD substance. If one accepts for the time being that the AD substance is of neurohypophyseal origin, the increased quantity in the blood must either be due to (*a*) increased production, and/or (*b*) diminished inactivation in the tissues. From our own studies we have no direct evidence against increased production. Gersh and Grollman (1939), however, could find no histological evidence of increased production in the posterior lobe of adrenalectomized animals—such as is found in dehydrated animals. On the other hand, some of our observations suggest that delayed inactivation of the ADH may be at least partly responsible for the increased titre in the blood. When hydræmia has been produced by a water load in adrenal deficient patients there is no prompt diuresis and the urinary AD activity during hydræmia is high. This could be interpreted as a failure of inhibition of the posterior pituitary secretion by dilution of the plasma electrolytes. But a phase of diuresis does occur later, and in the urine passed then, no AD substance can be detected. Inhibition of posterior lobe secretion would thus be taking place several hours after maximal hydræmia had passed. This seems unlikely. The time relations of diuresis to the ingestion of water would indicate that some processes are slow in adrenal insufficiency, and we suggest that inactivation of the circulating AD hormone is one of the processes which is delayed. Some confirmation of this idea comes from Gaunt's laboratory (Gaunt, 1949) where it has been shown that liver slices from adrenalectomized rats inactivate added Pitressin more slowly than does the liver tissue of normal rats. Gaunt *et al.* (1949) have also shown in adrenalectomized rats, and Lockett (1951) in adrenalectomized dogs, that there is an increased sensitivity to injected Pitressin—a sensitivity which could be explained on the basis of slow inactivation by the tissues of the AD hormone.

Effects of Cortisone and ACTH

The effect of injected cortisone on the water test has been observed in 2 patients with Addison's disease and 1 patient with hypopituitarism. ACTH has been used in 2 patients with hypopituitarism. Before treatment all patients showed failure of prompt diuresis after water; during therapy all patients showed a normal type of water diuresis.

In Fig. 1 is presented the result of a study in one of these patients, a woman with post-partum necrosis of the anterior pituitary. When water is given the diuresis is not prompt but occurs six to eight hours after the water load. The maximum fall in serum electrolytes takes place at the end of the second hour. Assay of the fasting serum reveals definite antidiuretic activity; assay of the serum taken at the end of the second hour—when the serum electrolytes are most diluted and when one would expect the posterior pituitary to have cut down its secretion substantially—still reveals considerable AD activity.

When 100 mg. of cortisone is given twelve hours before and another 100 mg. four hours before the test, the diuretic response to water is prompt. The level of the serum electrolytes falls maximally at the end of the first hour indicating an increased speed of absorption from the gut. Assay of the fasting serum shows no demonstrable AD activity. Nor was any significant activity shown in the serum taken when the dilution of the blood electrolytes was maximal.

Cortisone restores to normal the time of water diuresis and removes the increased AD activity of the serum. Leaving aside the improvement in absorption from the gut and the increased glomerular filtration—both of which are contributory to the restoration of normal diuresis—I should like to discuss in more detail the relation of cortisone to AD activity of the blood.

Cortisone is not diuretic by virtue of increased excretion of electrolytes; it is not diuretic unless water is given (Oleesky and Stanbury, 1951). It thus plays some part in restoring to normal the neurohypophyseal response to dilution of the blood electrolytes. It could do so by removing from as yet uncharacterized AD substance from the blood and allowing the normal mechanism of water diuresis to occur. It could also act by correcting some fault in the neurohypophyseal control of water.

In health two events must take place before water diuresis occurs: (1) secretion of the AD hormone diminishes or ceases; (2) AD hormone in the blood is quickly inactivated. Cortisone in restoring water diuresis to normal may act on one or both of these mechanisms. It may make hydræmia effective in reducing posterior lobe secretion or it may increase the rate of inactivation of the hormone in the tissues. At this point one must again refer to the later diuresis seen in the majority of patients with untreated adrenal insufficiency. As indicated before some process or processes concerned with water diuresis are slow when there is a lack of adrenal hormones. The speculation is made that one process involved is the removal of the AD hormone from the blood. In health this is known to be rapid. If, in adrenal insufficiency, it were slow it would permit accumulation of ADH in the blood and would explain the longer time necessary for inhibition of the posterior lobe to be manifest as a water

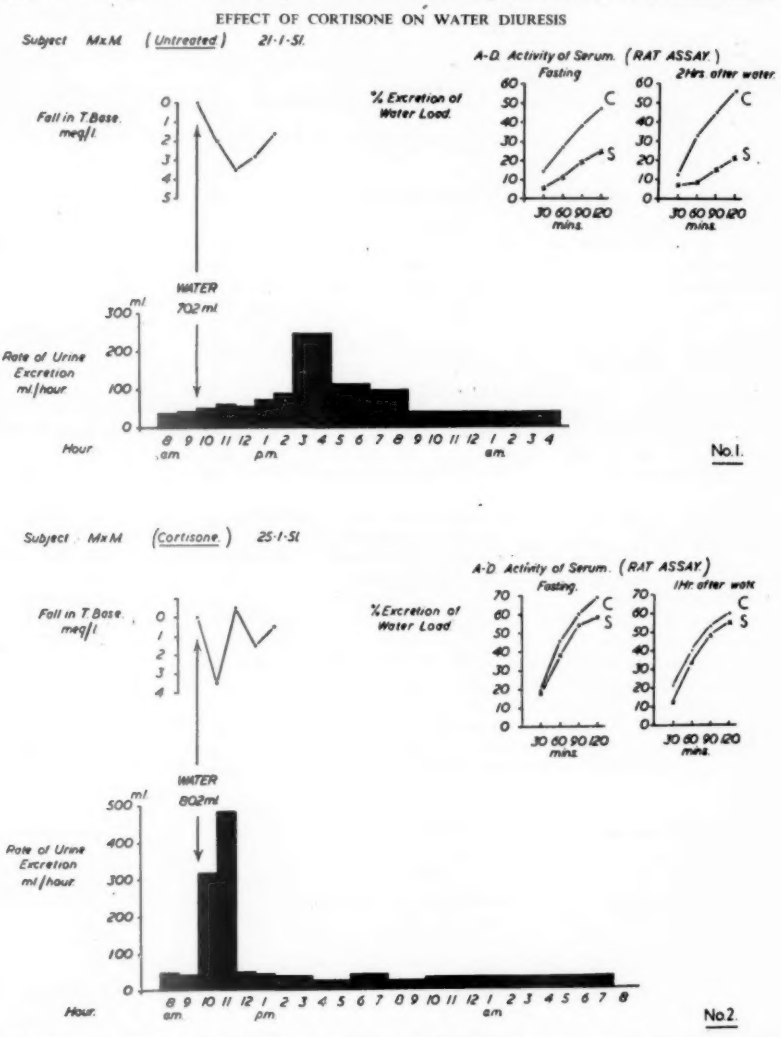

Fig. 1.—Kepler water test in a female patient, aged 44, with hypopituitarism. No. 1 shows delayed diuresis, slow dilution of serum electrolytes (total serum base) and AD activity of the fasting serum and of the serum taken two hours after water ingestion. No. 2 illustrates the effect of cortisone in producing a prompt diuresis, rapid fall in serum base and a disappearance of AD activity of the serum.
C = response in control animals injected with normal saline.
S = response in animals injected with patient's serum.

diuresis. Cortisone (1) reduces the quantity of AD hormone in the fasting blood, and (2) causes a prompt diuresis from a water load. Both these could be accounted for in terms of an increased rate of removal of ADH from the blood. A prompt diuresis is made possible by (*a*) hydræmia causing a reduction in output of ADH, and (*b*) cortisone hastening the destruction of circulating ADH to the normal rapid rate.

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Dr. R. A. Burston and **Dr. Oliver Garrod** (*Summary*):

Studying 5 patients with Addison's disease and 4 with panhypopituitarism, we found that the most obvious defect in renal function, failure of diuretic response to ingested water due to excessive tubular reabsorption, was present in each instance. Nor was this failure altered by adequate therapeutic control with desoxycorticosterone acetate, testosterone or thyroxine. In each patient the diuretic response to ingested water was restored by cortisone, confirming Thorn's earlier observation (1951). By injection, at least 100 mg. cortisone was required, the effect being evident twelve hours or more after the injection. Orally, 50 mg. had a similar though more short-lived effect, which became evident within three hours of ingestion of cortisone.

Glomerular filtration rate (GFR) and renal plasma flow (RPF) were found to be less than 50% of normal in 3 patients. Cortisone in the doses used raised both GFR and RPF, but not to normal levels. It is unlikely that this lowered GFR is the major factor in the failure of diuretic response to ingested water. Evidence was obtained that endogenous creatinine output varies with urine flow at all rates in the patients not receiving cortisone, suggesting that GFR is unduly labile in adrenal insufficiency.

The excessive tubular reabsorption may be in part due to excess antidiuretic hormone (ADH) activity, but is probably mainly due to renal tubular dysfunction which is restored by cortisone.

All patients gave evidence of abnormal renal tubular function after water ingestion when urine flow, urinary specific gravity and concentration of solutes varied very little for several hours, following which a delayed and partial diuresis occurred, with increased rate of urine flow, a fall in urinary specific gravity and concentration of solutes, probably due to release of ADH activity. The range of variation of these factors was restricted in every patient before cortisone was given, suggesting generally defective tubular function. Under the influence of cortisone normal prompt diuretic response occurred, with wide variations in rate of urine flow and urinary specific gravity. Thus cortisone restores renal tubular function to normal. Further evidence of the direct effect on renal tubular function was obtained in one patient in whom both the pituitary gland and hypothalamus were destroyed: an injection of 100 mg. cortisone produced a state of diabetes insipidus which lasted thirty-six hours, i.e. in the absence of cortisone diabetes insipidus was masked by renal tubular dysfunction.

[The full paper will appear in *Clinical Science*.]

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Section of Experimental Medicine and Therapeutics

President—Professor R. A. McCance, M.D., Ph.D., F.R.C.P., F.R.S.

[*December* 11, 1951]

WALTER ERNEST DIXON MEMORIAL LECTURE

[Number 6]

Some Problems in the Chemotherapy of Tuberculosis

By Professor Sir Howard Florey, M.D., Ph.D., F.R.C.P., F.R.S.

It was with particular pleasure that I accepted the honour of giving the W. E. Dixon Memorial Lecture, for as a young man I saw Dixon frequently in Cambridge. At that time the Pharmacological and Pathological Laboratories, of which only the façade now remains to remind one of the architectural oddities that were hidden behind it, adjoined one another and there was a common tea-room. At our meetings over tea Dixon's lively conversation animated not only pharmacologists but even the more lethargic pathologists, while the younger members at the tea-table were much influenced in their general attitude to experimental science by contact with such an active investigator and interesting personality. With those happy memories of Dixon it may perhaps be appropriate if I commemorate him by discussing some of the difficulties that meet those who are trying to find a successful method of chemotherapy for tuberculosis, for in chemotherapy many disciplines meet—those of the chemist, of the bacteriologist and mycologist, of the pharmacologist, sometimes of the pathologist and the clinician.

Practically all our initial knowledge of the chemotherapy of bacterial diseases, like so many other things in medicine, has been obtained empirically, and it would be a bold man indeed who would discourage or belittle this method of approach. Nevertheless perhaps the time is coming when we can supplement purely empirical methods with those based on knowledge of the behaviour of chemotherapeutic agents not only in the test tube but in the body. I do not propose now to deal with the mode of action of antibacterial agents *in vitro*. The problem, essentially biochemical, of their action upon the bacterial cell has proved to be of great complexity, and it is probably correct to say that in spite of much work we are still ignorant of the fundamental biochemical lesion produced in bacteria by any of the naturally produced antibacterial substances.

Mode of Action of Antibacterial Substances In Vivo

Relatively little attention has been paid to the mode of action of antibiotics in the animal body, so I propose firstly to discuss some of the phenomena associated with acute infections and their modification by antibacterial substances, and then to consider the more complicated conditions met with in tuberculosis. In spite of the degree of success that streptomycin and some other drugs have had, I suppose every clinician would agree that better antituberculous drugs are needed.

In searching for new antibiotics micro-organisms are examined for their production of substances that inhibit the growth of chosen bacteria or fungi. If an active substance is detected it is extracted, usually in a crude form, and produced in sufficient quantity to enable certain pharmacological tests to be made—especially regarding its toxicity. If it possesses no great toxicity its ability to inhibit the development of artificial infections in animals is examined. If these tests are encouraging the substance, after further purification and pharmacological investigation, is tried against infections in man. A similar series of investigations is carried out with synthetic substances suspected of being useful.

Although much attention is rightly given to investigations of the foregoing nature, little is usually given to consideration of the conditions that exist in the body during successful chemotherapeutic action.

The concentration of an antibacterial substance attained and maintained in the blood after parenteral or oral administration has, I think, rightly been taken as an indication of the concentration reached in normal body fluids. There is, however, an assumption here, and that is that the antibiotics of small molecular size such as penicillin and streptomycin pass freely to and fro through the walls of normal blood capillaries. This is probably so, but is by no means certain, as we have no knowledge of the effect of such factors as protein binding on any of the drugs in this connexion.

It is certain that inflamed vessels in lesions caused by pyogenic organisms become more permeable and easily let through even large protein molecules into the exudate of the lesion. Chemotherapeutic agents escape from the blood into these exudates and, what is most interesting, some can thereafter be detected in the exudates for a considerably longer time than in the circulating blood.

The causative organisms of the pyogenic infections are for the most part free in the tissue fluids or inflammatory fluids—indeed many virulent organisms are only with difficulty taken up by granulocytes in the non-immune animal. One can conceive, however, and it was indeed the first explanation given of the action of penicillin *in vivo*, that if the growth of an invading organism is stopped by a chemical agent the defences of the body, principally the phagocytes, then ingest and demolish the organisms and so protect the animal or cure the patient, as the case may be.

That such a process is possible was shown by Avery and Dubos (1931) before the introduction of the present effective antibacterial agents. They found that intraperitoneal injection of an enzyme that split the carbohydrate of the capsule of type 3 pneumococcus removed the capsules from the pneumococci, which were then ingested and destroyed by phagocytes, so that the body was protected from infection, whereas the encapsulated organisms were practically unaffected by the phagocytes.

Action of Penicillin and Other Antibiotics In Vivo

Views of the mode of action of penicillin *in vivo* changed when it was clearly demonstrated *in vitro* that penicillin killed most dividing organisms, though a few "persisters" sometimes remained. Recently the mode of action *in vivo* of some antibiotics has been investigated at Oxford by Gowans and by Bowden. The parenteral administration of penicillin, Terramycin and Aureomycin sterilized lesions caused by the intradermal injection of pneumococci into rabbits, treatment starting six hours after infection. Untreated animals died twenty-four to forty-eight hours after infection. This sterilization occurred even in rabbits freed from most of their circulating granuloctyes by the administration of benzol, and in which the migration of such cells into infected tissue was negligible. Most of the pneumococci quickly became Gram-negative and were dispersed into fine granular debris. Thus the effects on the pneumococci were independent of phagocytosis. It is interesting that under the same conditions of experiment large intravenous doses of Sulphamezathine failed to protect either normal or leucopenic animals from the pneumococcal infection. In mice infected intraperitoneally with pneumococci or streptococci penicillin, Terramycin and Aureomycin caused a rapid diminution of the bacterial content of the peritoneal cavity when treatment was begun twelve hours after infection. This diminution appeared to be unassociated with any increase of phagocytosis. Again Sulphamezathine was ineffective under similar conditions.

Thus there is some evidence that the antibiotics at present used in medicine owe their powers *in vivo* to their bactericidal properties and are not dependent on concurrent phagocytic activity, though this may at times be of some assistance.

Antibacterial Action in the Presence of Pus and Necrotic Tissue

It appears relatively easy to understand what happens during the chemotherapy of an acute infection, lasting a few hours or days, in which there is little or no tissue destruction. When there is tissue destruction with the ultimate formation of pus the picture is different. I was once optimistic enough to believe that penicillin could be made fully effective even in the presence of considerable slough and pus. Extended experience has shown that this is not the case, and it has also demonstrated that the more chronic the infection the greater is the difficulty of removing the infecting bacteria. This is well illustrated by osteomyelitis caused by the staphylococcus. If the disease is diagnosed early, before tissue destruction has occurred, the inflammation can be caused to regress by the

administration of penicillin alone. If an abscess has formed the pus must be evacuated in order to obtain a satisfactory chemotherapeutic effect. If bone has become chronically infected and there is dead bone present, no amount of penicillin, however administered, will sterilize the sequestra, and they must be removed surgically. The reasons for the failure of penicillin to sterilize slough or dead tissue are not clear, but the fact is worth keeping in mind as we go on to consider the possibilities of chemotherapy of tuberculosis, for penicillin in its own field is a very powerful bactericidal agent compared with the agents used against mycobacteria, and the lesions of tuberculosis nearly always contain necrotic tissue.

Tissue Reactions to the Presence of Myco. tuberculosis

I have mentioned at some length the possible behaviour of chemotherapeutic agents in the tissues in infections caused by bacteria that multiply primarily in extracellular fluid, to act as an introduction to the consideration of chemotherapy in the more complicated tissue reactions associated with the presence of tubercle bacilli. Perhaps I may be permitted briefly to recall the reaction that occurs in laboratory animals and in man to the presence of tubercle bacilli.

There is little if any direct evidence about the initial stages of the reaction to the presence of tubercle bacilli in man, but there is no reason to suppose that the reaction in man differs substantially from that produced for experimental purposes in guinea-pigs and rabbits. Jensen, Bindslev and Holm (1935) have shown that in the lungs of the previously uninfected guinea-pig inhaled bacilli can first be detected in mononuclear cells in the walls of the alveoli, in which they divide until a cell may contain as many as 30 to 40 bacilli. After a few days there is a sudden development of the cellular reaction and many cells of macrophage type appear. This reaction is greatly accelerated in the previously infected or "immunized" animal. When bacteria injected intravenously are arrested in the lung there is a somewhat fleeting polymorph reaction that is soon replaced by a collection of large mononuclear cells many of which contain tubercle bacilli (Vorwald, 1932). With the growth of the reaction it is supposed that more and more mononuclear cells appear and assume the somewhat specific form of epithelioid cells. At this stage it is probable that most of the tubercle bacilli are intracellular. With the growth of the tubercle, and the concurrent sensitization of the animal to tuberculo-protein, necrosis or caseation of the centre of the lesion occurs.

Observations In Vivo *of Vascular Reactions Around a Tubercle*

It is usually stated that a tubercle is avascular and published pictures of post-mortem injections of the blood vessels would certainly lead to such a conclusion. It is now possible to watch the development of a tubercle *in vivo* and so to follow early vascular reactions. Ebert, Ahern and Bloch (1948) and Ebert and Barclay (1950), who were the first to do this, have described the tissue reactions occurring when tubercle bacilli are introduced through a removable plug in the back of a transparent chamber in a rabbit's ear. We have been able to confirm the observation of Ebert and his colleagues that changes which are obvious under low powers of the microscope begin somewhere between the tenth and fifteenth days after inoculation, and thereafter advance with some speed. The first change to attract the eye under low magnification is the emergence of opacities in which it is difficult to make out cell details—indeed it is possible that many of the cells are dead. These areas extend until in a few days the tissue over the whole of the area under microscopic examination is necrotic. During this extension the blood-flow in the vessels at the periphery of the lesion, which are probably maximally dilated, first becomes slowed and usually oscillatory, and then passes on to stasis. The vessels containing blood in stasis become incorporated in the necrotic area and disintegrate. Leucocytes usually adhere in large numbers to the walls of the vessels near the tubercles.

The only substantial differences in the events seen in our chambers from those described by Ebert and his colleagues were that there was no increase of free tissue fluid during the growth of the tubercle, nor was dilatation of the blood vessels particularly noticeable. These slight differences were probably due to the layer of tissue being thinner in our chambers, and to its being more rigidly confined. Some chambers used by Sanders, Wells and Wylie (1949, unpublished) warped during their sojourn in the rabbit's ear so that the tissue became thicker than was intended. Tubercles growing in such chambers were surrounded by pulsating, widely dilated vessels, and much free fluid was present, as described by Ebert and his colleagues.

Penetration of Drugs into Tubercles

We are now in a position to appreciate how it is possible that the treatment of tuberculous infection by chemical means might have to differ from that of pyogenic infections.

There is little doubt that profound vascular changes occur around acutely developing tubercles, though these are probably not the primary cause of the necrosis which in this disease is commonly called caseation. It is clear, however, that drugs in the blood stream will have to penetrate considerable distances through necrotic and densely cellular tissue if they are to reach the bacilli that are often present in large numbers in caseous material, and that they must also be able to enter macrophages and epithelioid cells containing bacilli.

It is fairly certain that even the lesions that are detected at a so-called very early stage in man have usually evolved to the stage at which there is not only a substantial cellular reaction but also some necrosis. Many patients have extensive necrosis before it is recognized that they are ill, and great havoc can be caused in such an organ as the lung by chronic infection, marked by much fibrosis and cavitation, the disease gradually extending for many years.

The recognition as far as chemotherapy is concerned of the particular conditions existing in a tubercle is not new, and the problem was expressed very clearly by Wells and Long in 1932 before any antibacterial substances had been successfully introduced into therapeutics. They said:

> "If we wish to destroy the tubercle bacilli in the body by specific chemotherapeutic measures we must consider not only what chemicals can kill the bacilli in the test tube but also which ones can penetrate the tubercle and pass through the wall of the phagocyte in which they are so often entrenched";
>
> and
>
> "If the drug is to be a true chemotherapeutic agent in Ehrlich's sense, that is, a substance that kills bacteria and spares the host because it has a high selective affinity for the bacterial protoplasm and a low affinity for the protoplasm of the host, it must be able to penetrate the tubercle, the phagocytic cell if the bacilli are enclosed within cells, and the tubercle bacillus . . ."

Though the problem was thus clearly stated at least twenty years ago no particular attention seems to have been paid lately to the effect of the complicated structure of tuberculous lesions and the protected position of the bacilli, either inside phagocytes or buried in caseous material, on the possible therapeutic action of drugs *in vivo*.

The procedure adopted for finding agents active against organisms producing acute inflammatory lesions has been adopted in searching for drugs active against the tubercle bacillus. Thus natural antibiotics or synthetic substances are tested for their capacity to inhibit the growth of the tubercle bacillus *in vitro*; if they are active their toxicity is tested in animals, and if this is not too great they are tested for their effects on the acute tuberculous lesions caused by the injection of bacilli into experimental animals such as guinea-pigs or mice.

All the substances that are at present being tested for antituberculous activity are water-soluble and have small molecules, and one can conceive that after entry into the blood stream they spread more or less evenly in the extravascular fluids and possibly may also diffuse into caseous material and have some effect on the bacilli growing there. But such drugs do not necessarily penetrate into mononuclear cells harbouring bacilli. By a series of somewhat halting steps we have been led to examine in some detail the possibilities of bringing the drugs more closely to the bacilli.

Effects of Micrococcin on Tubercles

In 1948 Su, a Chinese bacteriologist working in Oxford, isolated from Oxford sewage a micrococcus which produced an antibiotic active against a number of Gram-positive organisms, the growth of some of them, for example the staphylococcus and streptococcus, being inhibited at a dilution as great as 1 : 30,000,000, though there was a considerable inoculum size effect and resistant strains could easily be produced. The tubercle bacillus was sensitive to the action of the antibiotic *in vitro* but much less so than the organisms mentioned. Micrococcin, as the substance was called, is remarkably insoluble in water. Heatley estimated that its solubility is of the order of 1 μg. in 1 ml. of distilled water, though supersaturated solutions can occur. The tubercle bacillus is not inhibited by a concentration of 1 μg./ml. and it is indeed difficult to fix a figure in the usual way. From the point of view of the experiments to be described it was sufficient to show that solid micrococcin applied to the surface of a culture medium inhibits the growth of the tubercle bacillus where the solid substance is placed.

The possession of this almost insoluble substance gave rise to the idea that it might be possible to induce monocytes and macrophages to phagocytose micrococcin, and so to concentrate it within the actual cells in which bacilli were living and dividing in growing tubercles. If this could be done the macrophages and possibly the epithelioid cells to which they give rise might be "fortified" by the antituberculous agent and thus might have their capacity to demolish tubercle bacilli, which is not naturally great, increased.

Indian ink was first used as a "model" for the behaviour of micrococcin, and was injected intravenously into rabbits with developing tubercles. If the ink was given within ten days of the intravenous injection of tubercle bacilli carbon particles were found in the epithelioid cells, and even in the caseous centre, of tubercles of liver, spleen and lung. When given later than ten days after infection, it only appeared in the tubercle in scattered macrophages. It seemed worth while, therefore, to see what effect micrococcin injected within ten days of infection would have on the development of experimental tubercles.

Firstly it was shown by a variety of means that the substance was innocuous when injected intravenously, subcutaneously and intrathecally in a finely particulate form into mice, guinea-pigs and rabbits, as long as care was taken not to introduce particles large enough to embolize large vessels in the lung or heart. The micrococcin was taken up by cells of the reticulo-endothelial system and some remained in the body for months, though it was gradually eliminated. It caused no apparent

damage to cells that had taken it up, whether connective tissue, macrophages, Kupffer cells or phagocytic cells of the spleen. It was easy to show that macrophages phagocytosed micrococcin locally applied in transparent chambers in the rabbit's ear. The follow-up of the fate of the micrococcin was facilitated by the fact that the substance fluoresces brilliantly in ultraviolet light.

Summarizing these preliminary experiments, it appeared that carbon particles could be introduced into tubercles from the blood stream if given soon enough after infection, and that micrococcin which was active against the tubercle bacillus *in vitro*, could be introduced into phagocytic cells without harming them. It seemed worth while to try to treat experimental tuberculosis by the intravenous injection of the particulate antibiotic.

The Failure of Particulate Micrococcin. Its Behaviour after Intravenous Injection

The first experiments were done on rabbits infected intravenously with bovine bacilli. With the dose of organisms used rabbits usually die in about thirty days. Later, guinea-pigs were used, a human strain of bacillus being injected intramuscularly.

The lives of the treated animals were not prolonged by frequent intravenous injections of finely particulate micrococcin, although the reticulo-endothelial cells of the spleen and liver were well filled with the drug. The development of the tuberculous process was slowed at first if the micrococcin was given soon after infection, for example on the fifth day, but eventually the lesions progressed as in untreated animals.

There were a number of possible explanations for the failure of the micrococcin to prevent the extension of the experimental tubercles. One was that the antibiotic did not in fact reach the cells that contained the tubercle bacilli. It was thought that some light might be thrown on this matter if the behaviour of the injected suspension of micrococcin in the blood stream were watched by ultraviolet light in normal uninfected tissue in a transparent chamber in the rabbit's ear. About one minute after the beginning of an intravenous injection, during which 10 to 20 ml. containing about 200 mg. of micrococcin were given in five to six minutes, fluorescent particles were seen passing along the vessels. These particles were much larger than those that had been injected. Although the fine particles were not agglutinated by serum they became caught up with blood platelets soon after they entered the blood stream and formed masses of the size of blood cells or larger. Few of the aggregates were large enough actually to embolize the small vessels, but they became adherent to the vessel walls where they showed as brilliantly fluorescent particles. The masses were found particularly in vessels of which the walls were "sticky", shown by the adhesion of leucocytes, such as are present in the growing edge of the normal tissue of a chamber.

These masses were not easily displaced and some remained attached to the vessel walls for days. Little if any of the substance was taken up by extravascular macrophages, although these were plentiful in the surrounding tissue, and only when the vascular pattern changed, as it does fairly often in growing tissue, did some become extravascular.

Some direct observations were made of the effect of intravenously injected micrococcin on a very young tubercle in a transparent ear chamber. Micrococcin particles adhered to the walls of the vessels that were patent alongside the growing tubercle, and much of this was still present in the same position after the vessels had thrombosed and been incorporated in the tubercle. All the same, it had no apparent effect on the growth of the tubercle, nor did it seem to be distributed in the phagocytic cells, even at the periphery of the lesion.

From all this work it was clear that the injection of this particulate antibiotic into the blood stream did not offer much hope of introducing it into the cells of a tubercle, so another approach, again with micrococcin, was made.

Effect of Micrococcin Dissolved with Triton

It had been shown long ago that vital dyes such as trypan blue, which form colloidal aggregates, could enter a tubercle and even stain the caseous centre, so an attempt was made to form a colloidal solution of micrococcin. Heatley found that Triton WR-1339, a non-ionic detergent which appears to produce no damage to an animal even after large amounts have been injected intravenously, can "dissolve" micrococcin, producing a solution with the consistency of dilute egg white when 5 mg. per ml. are present. The product is probably of the nature of a colloidal solution. Considerable amounts of this mixture could be injected intravenously, and after repeated injections fluorescent material could be recognized in Kupffer cells and cells of the red pulp of the spleen, where it remained for many weeks. There was evidence that a little of the micrococcin went into extravascular macrophages, but it scarcely passed out even from the very permeable capillaries of the gut, as little was found in the thoracic duct lymph of a rabbit.

The repeated intravenous injection of micrococcin-Triton solution into guinea-pigs with experimental tuberculosis produced no effect on the survival time of the animals or on the growth of the tubercles, and though many phagocytic cells containing micrococcin were visible at the periphery of tubercles in the spleen none was seen within them.

Penetration of Dyes into Tubercles

These experiments with micrococcin, though they failed in their primary purpose, have directed our attention to the state of the permeability of blood vessels around growing tubercles. In acute inflammation caused by pyogenic organisms blood vessels have their permeability greatly increased by the liberation of chemical substances by damaged tissues. We have seen that blood vessels can become involved in tuberculous necrosis, but what is their state in earlier lesions or before the necrosis reaches them? The fact that trypan blue and other vital dyes have been said to penetrate into rapidly growing tubercles suggests that the walls of capillaries are more permeable than normally. We have found that after even a single intravenous injection of Evans blue, which combines with plasma proteins, the dye leaves the blood stream and diffuses throughout a small tubercle. It seems probable, therefore, that in the neighbourhood of acute tubercles of animals the capillary endothelium is more permeable than normal, and this may well apply to man. What the state of the vessels is around the chronic lesions of man it is at present impossible to say.

The Effect of Tuberculin

The permeability of vessels near tubercles can be somewhat specifically increased by making use of the focal reaction that follows the intravenous injection of tuberculin. It is fairly clear that permeability is increased during a focal tuberculin reaction since exudates, presumably rich in protein, are formed. The increased capillary permeability following a tuberculin reaction can be demonstrated by vital dyes. For example it can be shown in guinea-pigs that considerably more dye appears around lesions caused by the intramuscular injection of BCG after an intravenous injection of Old Tuberculin than around lesions not subjected to the influence of tuberculin.

The question of the effect of tuberculin on vascular permeability, and hence on the access of drugs to tubercles, may be of some immediate interest, as already, though on other grounds, attempts are being made to enhance the effects of antibiotics such as streptomycin by the simultaneous use of tuberculin.

From these experimental findings and speculations it may perhaps be legitimate to suggest that the best type of chemotherapeutic agent for use in tuberculosis may prove to be one of large molecular size or attached to a large molecule, which would emerge from the blood stream where vessels were more permeable than normal and once having emerged would, like proteins, leave the extravascular fluid with difficulty except by way of the lymphatics. This advantage might be coupled with that conferred by the ability of macrophages to segregate and concentrate large molecular aggregates such as vital dyes, so that a high concentration of antibiotic might be produced intracellularly. No doubt small easily diffusible molecules may be effective in tuberculosis, as is shown by the results obtained with streptomycin, but these substances can diffuse in and out of lesions so freely that doses have to be frequently repeated and it is difficult to keep up an effective concentration especially in the interior of a lesion.

The Effect of Cortisone

There is now a considerable amount of evidence that cortisone will diminish the action of trauma and of certain chemical substances in increasing capillary permeability. There is probably a similar effect on the vessels around tubercles, for Ebert (personal communication) has demonstrated some remarkable alterations in the vessels of infected tissue in rabbit's ear chambers under the influence of cortisone. It is tempting to suggest that to regulate the access of a chemotherapeutic agent to tuberculous lesions one might increase and diminish the permeability of the surrounding vessels at will by the alternating use of tuberculin and cortisone. Unfortunately cortisone seems to have other effects in tuberculosis, for in both animals and man it appears to increase or even to provoke the spread of the inflammatory process.

Penetration of Drugs into Cells

You will remember that besides the question of penetration of a drug into the tuberculous lesion there was that of its penetration into phagocytic cells before or after they had acquired a population of tubercle bacilli. This can be envisaged as taking place in three ways—by the phagocytosis of particles, or by the selective uptake of large molecules analogous with the vital dyes, or by a less specific passage of substances through the cell membrane. This question has been investigated by Mackaness, who has devised an ingenious technique whereby it is possible to observe *in vitro* for many days the effect on tubercle bacilli that are contained within rabbit macrophages of drugs dissolved or suspended in the surrounding fluid medium. He will himself soon be describing his technique and the results obtained with it, but he allows me to give the following facts.

Inside a normal macrophage the coccobacillary forms derived from a three-weeks-old culture of virulent bovine bacilli (Branch strain) can be seen to be increasing in length after about twenty-four hours' incubation. At the end of forty-eight hours small cords of bacilli can be found in the cytoplasm, and soon after this sign of bacillary multiplication is seen, the macrophage dies and liberates the

bacilli into the surrounding medium. It seems possible that an insight may be quickly gained into the probable efficacy of an antituberculous drug in the whole animal by observing the behaviour of the intracellular parasite when the drug is present in the surrounding medium.

A number of substances have been examined. When in particulate form the substance micrococcin, which first initiated this work, was taken up by the macrophages, but the growth of bacilli, which was at first retarded by its presence, was not suppressed and the macrophages were eventually killed. The colloidal micrococcin-Triton preparation was little more effective, for at a concentration of 100 μg./ml. in the culture medium it only retarded death of the cells. In contrast to this a concentration of 10 μg. of streptomycin per ml. in the culture medium, but not 5 μg./ml., would inhibit the growth of the bacilli and preserve the life of the cells. We do not know much about the behaviour of streptomycin towards such cells, but it seems likely that it penetrates through the cell wall in a non-specific way.

It is thus possible to show that streptomycin can stop the intracellular growth of virulent mycobacteria, but even when growth is inhibited for many days the cells themselves are unable to kill the bacilli. They can, however, kill bacteria of the avirulent H37Ra strain in the course of a few days even without the aid of streptomycin. The human strain of tubercle bacillus H37Rv appears to be less sensitive to streptomycin than the bovine strain when inside macrophages.

In similar experiments to those mentioned above it has been shown that para-aminosalicylic acid cannot completely inhibit the virulent bovine bacillus even at concentrations of 100 μg./ml. Terramycin, on the other hand, is as active against intracellular as it is against extracellular bacilli. Complete inhibition is produced with this drug by a concentration in the medium of 12·5 μg./ml.

These experiments show that the concentration of streptomycin that has to be present in the fluid round the macrophages *in vitro* in order to inhibit the growth of intracellular organisms is considerably —of the order of at least ten times—greater than that required to inhibit the growth of tubercle bacilli in Dubos and Davis's fluid medium. In fact, growth is only fully inhibited by a concentration around the macrophages usually considered to be above that which can be maintained for any length of time in the body fluids. But of course we do not know what concentration of the drug is present at the point of action inside the cell.

It would seem that this method of examining antituberculous drugs may be of considerable value in estimating their possible performance *in vivo* as it separates out one factor for study, namely the behaviour of the drug towards intracellular bacilli. We do not, of course, know whether the cells, which remain actively motile *in vitro* for many days, retain all the properties they possess in the intact body, but there are no reasons to suppose that they do not.

Desirable Properties in a Chemotherapeutic Agent

With these experiments and speculations in mind perhaps one may attempt to define the qualities that might be worth looking for or incorporating in substances to be examined for their antituberculous action *in vivo*. One can, as is usually done at present, look for easily diffusible substances of small molecular size. If sufficiently non-toxic and frequently administered such a drug might be quite satisfactory. But another possibility exists, and that is, to use substances of relatively large molecular size, or substances firmly bound to large molecules, which do not diffuse readily from normal blood vessels but which could be made to enter tubercles somewhat selectively by their capacity to pass through the walls of capillaries whose permeability is increased. To give any hope of usefulness such a substance should be able to inhibit the growth of the tubercle bacillus *in vitro* at great dilution, should for preference be bactericidal rather than bacteriostatic in low concentrations, should be able to penetrate macrophages and possibly epithelioid cells, and should be concentrated by these cells in the manner of a vital dye. It would be highly desirable that the tubercle bacillus should only acquire resistance to the drug slowly, if at all, for under the best conditions likely to be attained treatment of established tuberculosis must still be prolonged, and therefore the bacillus would be subject to the action of the drug for a considerable time. The drug would, no doubt, be segregated by cells of the reticulo-endothelium such as are present in the spleen and liver. As it would remain in these and other parts of the body for a considerable time it would need to have low toxicity for cells in general, and in particular for the kidneys, liver and other organs where it might be concentrated. Also it must not be carcinogenic. At present I know of no compound having these properties. I put forward these propositions in case among the many thousands of synthetic compounds that have been and are being produced, and among the many antibiotics that are being extracted, one or more may be found to have at least some of the required properties, so that the proposals can be tested.

Treatment of Human Tuberculosis

Supposing that one could successfully achieve in experimental animals cure of tuberculous infection on the lines that I have suggested, would all be set fair for the treatment of human tuberculosis? I very much doubt it.

It may be useful to emphasize again that the lesions in animals on which drugs are tested are of a relatively acute nature, but that most lesions in man are chronic. They are characterized by necrosis, sloughing and liquefaction, and fibrosis. In the lungs cavities which usually communicate with bronchi are formed. Bacilli may grow in enormous numbers in the slough lining the cavities. To accomplish the eradication of bacilli from such lesions and to secure complete healing is indeed a formidable undertaking. It is unfortunate that the ability of the body to dispose of necrosed tuberculous tissue is so poor, and that liquefaction of a necrotic focus often seems to produce conditions favourable for the growth of the tubercle bacillus.

As I have already mentioned, there are good reasons for believing that the presence of slough or pus that cannot escape to the exterior hinders or prevents the sterilization of staphylococcal lesions by penicillin even though the organisms are to a considerable extent extracellular. It is probable that much the same applies to the treatment of tuberculosis in which slough, represented by tuberculous caseation, is present.

Some experimental evidence is to hand to support this view. Steenken and Wolinsky (1950) pointed out that the abscess that forms in a guinea-pig at the site of injection of tubercle bacilli, and at times the abscesses in the regional lymph glands, are not sterilized even after the uninterrupted administration of streptomycin for 528 days. When these abscesses discharge or are drained healing is likely to occur. These authors also studied the chronic lesions that occur in immunized guinea-pigs or follow the suppression of lesions for some time by streptomycin. In one experiment the disease was allowed to progress for 96 days and then treatment with streptomycin was given for 300 days. Of 7 animals killed at the end of treatment 3 had gross lesions consisting of cyst-like structures, in the liver, spleen and lungs, teeming with bacilli that had acquired no significant resistance to streptomycin. The authors point out that this contrasts with the uniformly successful suppression by streptomycin of the acute form of the disease in guinea-pigs. One might well despair of being able to do much with chronic tuberculous lesions in man if it were not for the fact that we know that healing of extensive lesions can occur without chemotherapy, and that the tendency to healing is nearly always strong.

There is one conclusion that can be drawn with great force from these considerations, and that is that early diagnosis and treatment of tuberculosis are absolutely essential for the really successful use of a chemotherapeutic agent. The smallest lesions of active tuberculosis that are now clinically recognizable have almost certainly undergone necrosis, so that even in these treatment will have to be continued for a long time to allow of full healing.

One could perhaps go so far as to conceive of a drug so little toxic to the body that it could be used periodically as a prophylactic in very much the same way as antimalarial drugs are used at the present time. At present we are far from this goal.

It is clear that much remains to be done in understanding the problems of chemotherapy even of experimental tuberculosis in animals. Progress is being made, however, and if any of the experiments I have mentioned or suggestions I have made lead to further experiments I shall be very grateful.

In this lecture I have used freely the results obtained by many colleagues in my department. In particular Drs. Markham, Mackaness, Sanders, Heatley, Wells and Dodson have done much of the experimental work I have mentioned. I am greatly indebted to them.

Perhaps Dixon would be pleased to see how in these days pharmacological investigations have a more and more potent influence on therapeutics, how in certain directions the findings of the pharmacologist may with profit be integrated with those of the pathologist, and how the combined observations of the two may directly concern those whose primary interest is the care of patients.

[The lecture was illustrated by slides.]

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Section of Comparative Medicine

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Brucellosis in Animals and Man

PRESIDENT'S ADDRESS

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BRUCELLOSIS in animals leads to great loss of milk and of offspring and to subsequent infertility; factors which contribute largely to a low standard of nutrition and living in the countries affected. The direct effects on humans are also of great importance because, although mortality is low, brucellosis causes much long-continued sickness and incapacity, especially in countries where conditions are conducive to widespread human infections and where these are with the more virulent species of brucella. In *Br. abortus* infections it is the economic aspects which predominate, though much sporadic human illness is caused. In *Br. melitensis* and *Br. suis* infections, human illness and inability to work assume greater importance.

PREVALENCE

In most countries brucellosis is not yet a notifiable disease in man or animals and realistic estimates of its prevalence are difficult.

Animals.—In many European countries *Br. abortus* infection in animals reaches 10 to 20 or 30% and similar figures have been reported for certain countries of South America. In the United States of America the latest figures give about 16% of herds infected and 4% of cows. In the Scandinavian countries infection was present to a similar or lower degree, but is now absent from Norway and much reduced elsewhere. Estimates of its prevalence in Great Britain are complicated at the present time by widespread vaccination. Before governmental measures were taken for its control a survey made by Lovell and Hill (1940) showed that of 30,892 pregnancies, 9·7% ended abnormally—5·4% in abortion and a further 4·3% with a dead calf; and from collateral evidence it is fairly certain that most of the abortions and many of the dead calves were due to brucella infection. Other data showed that about 20% of adult female bovines had brucella antibodies in their blood. *Br. melitensis* infections in goats and sheep are known to be widespread in many countries of the Mediterranean and Latin America, whilst *Br. suis* infections are common in certain areas of the United States of America.

Man.—Dissatisfaction is also often expressed with the data available with regard to infections in humans, but the figures published by the World Health Organisation in their Epidemiology and Vital Statistics Reports are of interest. The figures for 1950 (Rep., July 1951*a*) include the following: Canada, 249, U.S.A. 3,163, Mexico (for 1949) 1,435, Peru 587, Western Germany 201, Denmark, 188, Spain 4,803, France 1,439, Greece 93, Italy 9,538, Malta 834, Holland 34, Norway 3, Sweden 16, Switzerland 169, Australia 39, New Zealand 42. Figures for previous years are similar except in the case of Norway, Sweden and Denmark where they were much higher.

In general, the number of undiagnosed and unreported cases is probably much higher than indicated by these figures; for the United States of America and France, e.g. estimates based on detailed examination of certain areas have put the probable totals at 40,000 to 100,000 for the United States of America and 9,000 for France respectively. In one of their earliest reports the Montpelier workers reported that in a number of communes in which they examined all the people they found 2 to 18% infected (Taylor *et al.*, 1938). As regards Great Britain, Wilson in 1932 suggested from his sample testing, a figure of 400–500 cases per year. Dalrymple-Champneys (1950) believes this estimate to be too low.

SPECIES OF BRUCELLA AND THEIR DISTRIBUTION

Reference has been made to three species of brucella, viz. *Br. melitensis*, *Br. abortus* and *Br. suis*. Their main distinguishing characters are shown in Table I, and most strains—provided they are in the smooth phase—show both the biochemical characters and the serological characters of one or other of the species. Strains with the biochemical characters of *Br. abortus* and the serological characters of *melitensis* have, however, been reported in France, India and Great Britain, whilst strains with the opposite characters occur in Italy (private communication). Recently, moreover, in

our capacity as one of the WHO Brucellosis Centres, we have received at Weybridge type strains from certain other Centres, and I have been surprised to find that certain type strains of *abortus* and *suis* from other Centres have the serological characters of *melitensis*, whilst one *melitensis* type strain has the serological characters we associate with *abortus*. This may be one of the vagaries of chance but it suggests the desirability of further examination of the characters of a number of strains from widely separated areas and correlation of their *in vitro* characters with the epidemiological and clinical features of the infections concerned. In addition to the characters shown in the table the three species show differences in their pathogenicity for the guinea-pig.

Br. abortus occurs mainly in cattle, *Br. melitensis* in goats and sheep and *Br. suis* in pigs but any of the species can occur in man and almost all of the domesticated animals. Distribution in respect of animal and country is mainly as follows: *Br. melitensis* in goats in Mediterranean countries and in South America (Argentina), in sheep in Mediterranean countries, and in cattle in the latter and also in the United States of America where it also occurs in pigs; *Br. suis* in pigs in the United States of America, and *Br. abortus* mainly in cattle and in nearly all countries.

TABLE I.—DIFFERENTIAL CHARACTERS OF BRUCELLA

	Br. abortus	*Br. melitensis*	*Br. suis*
Aerobic growth	−	+	+
H_2S production	++	− (or trace)	++++*
Growth in presence of Thionine ..	−	+	++
Growth in presence of Basic fuchsin ..	++	+	−
Agglin. in mono-specific sera for *abortus* ..	++++	−	++++
Agglin. in mono-specific sera for *melitensis*	−	++++	−

*Strains isolated in Denmark did not produce H_2S.

The number of + signs indicates: *for H_2S production*, the amount and duration; *for dyes*, the relative amounts of growth; *for agglin.*, the number of tubes showing agglin. in an ordinary doubling series.

In Great Britain our only important problem is *Br. abortus*. *Br. suis* does not occur. Strains with all the characters of *Br. melitensis* are isolated occasionally but no single case of human disease has been associated with them, although in many instances milk from infected cows has been drunk in the raw state, and cows have aborted and been handled in the usual way. It is interesting to speculate whether the accepted *in vitro* characters of *Br. melitensis* are in this case unassociated with the usual pathogenicity or whether it is a question of dose, as was first suggested by Alice Evans to account for the sporadic nature of *Br. abortus* infection in humans and the almost epizootic nature of *Br. melitensis* in certain areas. It is of interest to recall, on the other hand, the work of Meyer and Eddie (1941) who analysed 34 laboratory infections and found 21 were with *Br. melitensis*, 12 with *suis* and only one with *abortus*. Opportunities for actual contact with infected material and degree of personal hygiene of course play a part, but there seems no doubt that *Br. melitensis* is much more infective than *Br. abortus*, with *Br. suis* intermediate.

A curious fact is that, whilst *Br. melitensis* is widespread in sheep in some areas of Southern France, sheep in frequent and close contact with infected goats in Argentina do not appear to contract the infection. Further work on this and similar circumstances would be of interest.

ON INFECTION AND SPREAD, PATHOGENESIS AND EPIDEMIOLOGY

It has been shown that cattle can be infected by ingestion (Birch and Gilman, 1925), by way of the conjunctiva (Thomsen, 1918; and Schroeder, 1922), by way of the skin, broken or unbroken (Hardy *et al.* 1929, Bang and Bendixen, 1931) and also *per vaginam* (Bendixen and Blom, 1947; Manthei, 1950) as well as by injection; and it is probable that most species can become infected by any one of these routes. It is also known that guinea-pigs can be infected by inhalation of quite small numbers of brucella, and infection may occur thus in other animals and in humans. The actual route will depend largely on the kind of exposure.

The source of infection in animals is usually an aborted fœtus or the infected genital discharges or urine, though it is likely that, on occasion, infection occurs in the process of milking.

In humans, contact with infected materials such as a fœtus, placenta, urine, manure or carcases is a common cause of infection in exposed people, e.g. veterinarians, farmers, cowmen and all who handle animals or their products. In some countries it is believed to account for 40–70% of cases. Ingestion also plays a considerable part, the main source of danger being raw cream and milk and certain products made from them, such as soft cheese. Viable brucella have also been found in infected carcases after a period of a month in cold store and after moderate pickling but these are not likely common sources of infection. Salads made from wild greens contaminated with infected goat or sheep excreta have also been incriminated in human infection. It is also believed that infection may be dust or droplet borne and infect via the eye or respiratory tract. Accidental inoculation has also occurred in the laboratory and in the field. Personal hygiene, environmental sanitation and heat treatment of suspect foodstuffs are methods of preventing infection.

Whilst certain aspects of the development of the disease are similar in all species, e.g. the initial bacteriæmic phase, the distribution of infection in the lymph nodes, in the reticulo-endothelial system in general, in the spleen and liver, there are marked differences in other respects. Thus, in cattle, sheep and pigs a characteristic placentitis occurs and is followed by abortion or premature parturition, whereas in humans abortion is rare. Again, in *Br. suis* in pigs, abscess formation, e.g. in the vertebral column, is a common feature, but never occurs with other species. Mammary infection is usual in animals but appears to be rare in humans. Whether the cow, goat, sheep or pig suffers from the lassitude, chills, headache and other pains associated with the human disease, we shall probably never know, but they show little evidence of these symptoms in the way of drop of milk yield and loss of flesh, though some pyrexia occurs soon after infection.

The incidence of infection in the human female and in the young is much lower than in males and there seems no doubt that this is due to a greater resistance because, though the peak age for male infection, 30–35 or so, is also one during which exposure might be highest in some respects, the reports of the Montpelier workers (Taylor *et al.*, 1938) made it clear that in the area in which they worked, the "stable" was virtually a part of the house, and the children and women were exposed equally with the men.

In animals it is almost impossible to compare sex rates because of the small proportion of males kept and the much lower degree of exposure to infection. The resistance of the calf to infection is, however, undoubted and the young of other domesticated species are probably similarly resistant.

Control of Brucellosis in Bovines

Methods of control fall under three headings: those based on the elimination of infected animals detected by the agglutination test, those based on vaccination, and those in which the two methods are combined.

Segregation, Sale and Slaughter of Animals Reacting to the Agglutination Test and Sanitary Measures

This subject has been studied for the last forty years and the literature shows here and there numerous reports referring to single herds or small numbers of herds. Control and eradication by this method has, however, only been put into operation on a large scale in a small number of countries, notably Norway, Denmark, Sweden, Finland, the United States of America and Canada, though projects of considerable size have been undertaken in certain other countries, e.g. parts of Germany and Palestine.

Norway.—In Norway a scheme for the eradication of the disease was introduced in 1934 when a series of simple but effective laws were passed. In essentials these stated that aborting animals must be reported and tested, and that the owner of infected animals must not allow his animals to have a chance of infecting those of other owners through sale, service or contact of any kind whether on the home farm or on the common pastures which are characteristic of much of the Norwegian agricultural areas. Infected animals were marked and could only leave the farm for slaughter (when compensation was paid). In 1936 there were 2,758 infected herds. The disease has now been eradicated. Some setbacks were met but only some 2–3% of herds accepted as "clean", "relapsed" or became reinfected.

Denmark.—Eradication has also made great headway in Denmark, the percentage of herds free from infection being as follows: 1946, 32·9; 1947, 67·3; 1948, 77·3; 1949, 86·9; 1950, 89·6. It is noteworthy also that during the last five years cases of human brucellosis have been 0·7 per 10,000 inhabitants (1949 e.g. 194 cases) or about half the rate for the 1931–40 period. Calf vaccination is now used as an adjunct to other methods.

Sweden.—In Sweden the national campaign against brucellosis was begun in 1938, when 5·5% of their cattle were infected. At July 1951 the corresponding figure was 0·4% or 1,677 animals out of a total of 370,000 in the country. Reported cases of undulant fever have dropped from 114 in 1939 to 16 in 1950.

Finland.—In Finland also great progress was made until the war caused much uncontrolled movement of animals and a resultant serious setback.

U.S.A.—The Federal project for the eradication of bovine contagious abortion from the United States of America was begun in 1934. It was then estimated that 10% of cattle were infected. The project was difficult to apply in certain herds and certain areas, whilst new outbreaks of the disease occurred in 2–5% of the free herds. In 1949 tests on over 5 million animals showed 4% to be positive to the agglutination test, whilst the corresponding figure for 1950 was 3·5%.

During this time the value of Strain 19 vaccine had become established and at the present time three methods of control are officially approved: (*a*) Test and slaughter of reactors; (*b*) test and slaughter, with calf vaccination; and (*c*) test and conservation of reactors with calf vaccination. Indemnity is paid for slaughter under methods (*a*) and (*b*). Vaccination of the whole herd, i.e. including the adults, has become more common, particularly in certain types of herd and in certain areas. It is not, however, encouraged officially because the agglutination reaction which follows vaccination of adult animals interferes with subsequent employment of the agglutination test for eradication purposes. Official opinion in America still has as its goal the complete eradication of brucella infection.

Great Britain.—In Great Britain there has never been any official project for eradication on the basis of the agglutination test, although some investigations with the possibility of this in view were made between 1930 and 1940. These comprised about 140 herds. No general report was made but I was myself responsible during that period for some 50 herds. In 19 herds which were under control for four to five years the average incidence fell from 20·5% to 0·4%, whilst at the end of two, three, four and five years respectively, 6, 11, 12 and 15 herds respectively had been freed from the disease. In general, abortions due to brucella ceased within one year and remained absent until 1940 when observations were discontinued; it is known, however, that several herds became infected in the next five years and three major breakdowns with numerous abortions occurred. Reduction of infection in the other herds was somewhat similar up to the time the work ceased.

The general conclusion to be drawn from the results reported in different countries is that control by elimination of reactors to the agglutination test and sanitary measures is practicable in individual herds and in large areas or whole countries, but that it can be followed by serious disasters if infection is reintroduced into a herd which is free and in consequence highly susceptible. It can be recommended only on farms and in a country where the general level of hygiene is good, where the veterinary services of the country are such that proper supervision and blood-testing services can be maintained and where the animal owner and attendant can be educated to avoid the accidents which may otherwise occur.

Vaccination

Most investigators have done their preliminary experiments on vaccination in guinea-pigs and the literature on the subject is large. Huddleson (1924, 1929) in America in the early 1920s appears to have been the first to suggest that attenuated strains of *Brucella abortus* might resolve the problem of control in the bovine. Unfortunately, the strain with which he did most of his work did not confer sufficient resistance. Cotton (1932) and Cotton, Buck and Smith (1933, 1934) at about the same time compared the vaccinating powers of various strains of low virulence and eventually selected one, the now well-known Strain 19, because of its stable character and high immunizing power. Buck (1930) also showed that a satisfactory immunity can be estabished by vaccination at the age of about 6 months and that animals so vaccinated usually lose their agglutinating antibodies by the time of their first calving. This fact made this method of vaccination fit well with the eradication project to which the American authorities were committed and from 1936 onwards interest in that country centred on the employment of S.19. In both Denmark and Germany work has also been carried out with Strain 19 or with other strains of attenuated virulence.

At about the same time, McEwen (1937, 1939, 1940 and 1941) at Wye in Great Britain, in his classic studies in guinea-pigs and cattle, showed that the rough strain, 45/20, used in 2 doses, conferred adequate immunity without the production of agglutinins. Several experiments showed the undoubted immunizing power of this strain but unfortunately it was also shown that this strain could revert to a virulent form with the result that its use has now ceased.

During the same period Gilbert (1943), working at Weybridge, made a number of investigations with a dead vaccine composed of virulent brucella killed with formalin and suspended in an oily vehicle (Stableforth, 1947). After many experiments with different doses, vehicles and sites of injections it was found that a dose of 600,000 million organisms in 5 c.c. of 10% lanolin in paraffin conferred a high degree of immunity against a dose of *Br. abortus* which caused most unvaccinated animals to abort. The vaccine, being dead, is safe and it can also be stored. The large number of bacteria required make it, however, more costly than a living vaccine such as S.19, whilst the protection conferred is less powerful.

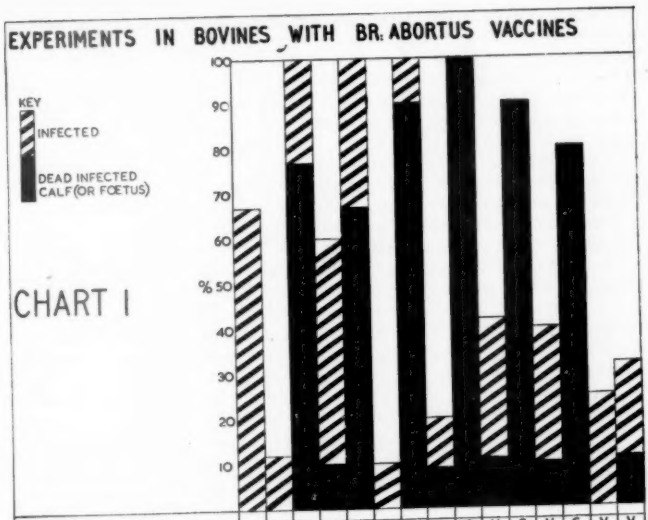
It was also shown by Paterson, Pirie and myself (1947) that a fraction with considerable immunizing power for guinea-pigs could be obtained from *Br. abortus* by extraction with 2% phenol and subsequent ultra-filtration and ultra-centrifugation. A similar fraction, however, conferred no protection in cattle (*see later*).

Huddleson (1946) has also in recent years prepared a vaccine containing brucella in the " mucoid " phase but cattle experiments have not so far shown it to be of great value.

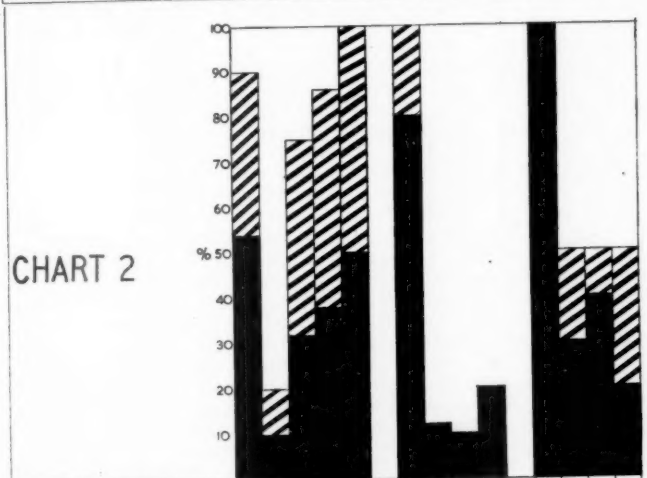
Before referring to our own work and experience with the above vaccines, reference should be made to experimental work done elsewhere with S.19 vaccine. In the U.S.A., Cotton, Buck and Smith (1934) carried out a number of experiments with Strain 19 including, according to Mohler, Wight and O'Rear (1941), 70 vaccinated calves and 73 unvaccinated controls: of the 70 vaccinated animals only 8 (11%) became infected after an exposure to infection which caused infection of 57 of the controls (78%), and of these 55 aborted or had premature calves. Thomsen (1939) in Denmark tested the vaccine in 6 herds, two-thirds of which were vaccinated and one-third left as controls. Of 266 vaccinated animals, 3·3% aborted whilst nearly 92% calved normally. Of 135 controls 25·1% aborted whilst 66·1% calved normally. In both cases some results were excluded as "uncertain".

Results obtained in Great Britain up to date with all these vaccines are shown side by side in the charts. Those made with killed vaccines were carried out at Weybridge, all the remainder at the Field Station of the Agricultural Research Council at Compton (Edwards *et al.*, 1945, 1946; McDiarmid, 1949, 1950).

In all of these experiments except the last the animals were vaccinated about two months before service and the challenge dose was administered at about the fifth month of pregnancy. This challenge



CONTROL OR VACCINATED	C	V	C	V	C	V	C	V	C	V	C	V	C	V	V
VACCINE		S/9		S/9		S/9		S/9		K		K		K	K
DOSE X 10^9		120		120		60		60		10*		10 M		10 M	500
ROUTE		SC.		SC.		SC.		SC.		SC.		IM		IM	IM
CHALLENGE DOSE	1·5	1·5	150	150	15	15	150	150	30	30	15	15	15	15	15
PROPORTION INFECTED	6/9	1/8	9/9	6/10	9/9	1/9	9/10	2/10	3/3	4/9	9/10	4/10	8/10	2/8	3/9
% INFECTED	67	12	100	60	100	11	100	20	100	44	90	40	80	25	33
PROPORTION DEAD CALVES	0	0	7/9	1/10	8/9	0	9/10	1/10	3/3	1/9	9/10	1/10	8/10	0	1/9
% DEAD CALVES (OR FŒTUS)	0	0	78	10	67	0	90	10	100	11	90	10	80	0	11



CONTROL OR VACCINATED	C	V	V	V	V		C	V	V	V		C	V	V	V
VACCINE		S/9	K	K	FR			S/9	S/9	S/9			S/9	S/9	S/9
DOSE X 10^9		60	600	60	•60			60	24	12			60	24	24
ROUTE		SC.	IM.	IM.	ID.			SC.	ID.	IC.			SC.	SC.	ID.
CHALLENGE DOSE	150	150	150	150	150		150	150	150	150		150	150	150	150
PROPORTION INFECTED	10/11	2/10	7/9	7/8	10/10		12/12	1/8	1/10	2/10		10/10	5/10	5/10	5/10
% INFECTED	91	20	78	88	100		100	13	10	20		100	50	50	50
PROPORTION DEAD CALVES	6/11	1/10	3/9	3/8	5/10		10/12	1/8	1/10	2/10		10/10	3/10	4/10	2/10
% DEAD CALVES (OR FŒTUS)	55	10	33	38	50		83	13	10	20		100	30	40	20

dose was always prepared with the same strain, *Br. abortus* 544, which is maintained at Weybridge in the dried state and has been used for all our tests of immunity in guinea-pigs, goats and cattle since it was first titrated by McEwen and his colleagues (1939).

It will be seen that, with the exception of the first experiment in which a dose of 1·5 millions proved too small, the experiments were made with either 15 millions (most of the earlier experiments) or

150 millions, and that the results in unvaccinated controls are reasonably consistent. The 150 millio dose has been used ever since we first learnt that animals vaccinated with S.19 would usually sta up to this exposure.

The strain used in the earliest experiment 45/20 (Chart 1) produced a satisfactory degree resistance but, as stated earlier, it mutated (Taylor and McDiarmid, 1949) and is no longer use The killed vaccine protected well against a test dose of 15 millions (Chart 1), but (Chart 2), even a dose ten times that of S.19, broke down when challenged by a dose of 150 millions. The brucell fraction used in the experiment shown produced little or no increased resistance. S.19 conferre a consistently high level of protection in all except the last experiment.

The last two experiments in Chart 2 are concerned with route of vaccination. It is seen in th penultimate experiment that 2,400 million organisms injected intradermally or 12,000 million intra caudally (into the dense tissue under the tail) protected about as well as 60,000 million organism subcutaneously. It was thought, however, that this latter dose might have been unnecessarily larg and the last experiment (not yet published) was intended to test this point. Unfortunately, no grou showed the degree of protection found in earlier experiments and, though no difference is seen betwee the three groups, the results are not satisfying. It is interesting that, contrary to usual practice, th animals were vaccinated shortly after service, a fact which may have contributed to this result. Th tests of the vaccine made in guinea-pigs did not suggest that the vaccine itself was deficient since th results were well up in the 60–80% protection range characteristic of vaccinated guinea-pigs whe challenged with the standard dose of 5,000 virulent brucella.

Vaccination under natural conditions.—There are many reports on the results of the use of S.19 i cattle under natural conditions; usually without unvaccinated controls. Large experiments both i the United States of America and in New Zealand have given satisfactory results, whilst our own experience in Great Britain (Lawson, 1950) has been favourable. There have been and still are herd in which results have not been satisfactory and sometimes no reason whatever can be found but there is no doubt that the loss from abortion due to all causes has fallen greatly, probably to abou 2%, whilst that due to brucella has dropped to an even lower figure.

*Duration of the resistance conferred by S.*19.—There is not yet sufficient information regarding the duration of immunity either for animals vaccinated as calves or for those vaccinated later in life. There are some reports concerning animals vaccinated at 4 to 8 months which suggest that, whilst immunity may already be diminished a little by the second calving, it will be adequate for most natural exposures. There is other evidence that it has considerably decreased by the third pregnancy. There is also information from an investigation carried out over eight years and covering 157 pregnancies in vaccinated animals and 91 in controls (the vaccinated and control animals being kept together in yards and exposed to heavy natural infection), that immunity in the vaccinated animals was adequate for the first three pregnancies but had fallen heavily by the fourth pregnancy. These results are in agreement with various observations made under field conditions. In general, all the information supports the view that immunity gradually decreases unless the animals are exposed to natural infection whilst they still have some immunity from the original vaccination.

Experiments designed to determine more exactly the duration of immunity are in progress in the United States of America and in Great Britain (Compton) and in the latter attempts are also being made to determine the best methods of vaccination and revaccination.

Stability and safety of Strain 19.—Although there can be no certainty that a living agent will never change, Strain 19 has so far proved remarkably stable. It dissociates unless stock cultures and vaccines are made under proper conditions. If properly maintained, however, there seems no doubt that it is stable, without danger to other animals, and conserves its power to immunize well. In America, there appears to have been no change since it was first isolated in 1925 and our own experience at Weybridge with tests on each batch of vaccine over the last eight years has shown no change either in its virulence or its power of immunization. Moreover, no change in virulence occurred either in America or in Great Britain when the strain was submitted to conditions which would favour such a change, viz. passage in the bovine (Mingle, Manthei and Jasmin, 1941; Taylor and McDiarmid, 1949). In both countries, a normal pregnant heifer was made to abort by the intravenous injection of a very large dose of Strain 19; and in both cases the brucella obtained from the fœtus were passaged by the intravenous route through six, or in the British case, seven further animals.

In all the literature there are only one or two reports of Strain 19 having been recovered at the time of calving even from animals exposed to heavy experimental infection or of the recovery of this organism from milk. Moreover, there is no evidence that susceptible animals, kept in contact with animals which have been vaccinated in the ordinary way or which have aborted following intravenous injection during the period of gestation, have ever contracted infection. The vaccine, being living, has a relatively short life unless it is freeze-dried, when it can have a life of over a year.

There are many other practical matters concerned with the use of S.19 vaccine with which it is not possible to deal here. The fact that resistance remains long—how long is not yet known—after the agglutination reaction caused by the vaccine has disappeared, is a point of some interest, as is also the interdependence of the age of vaccination, extent of agglutination response and duration of immunity. The nearer an animal is to puberty the longer does the agglutination titre remain above

rmal and—it may be guessed—(though it is not dependent on titre) the longer and stronger will the immunity. The persistent agglutination reactions are of no practical importance in themselves t are a serious disadvantage where vaccination is being combined with elimination of infected imals on the basis of blood tests, because there is no way of distinguishing them from those used by natural infection with virulent strains.

S.19 is an extremely valuable vaccine but work is still going on to find a better means of protection.

Control of Brucellosis in Other Animals

Brucellosis does not occur in pigs, goats or sheep in Great Britain. Vaccination has not proved tisfactory in pigs, and control depends, therefore, on segregation and elimination of infected imals. This is complicated by the fact that whilst the agglutination test is effective as a herd test, is less so in individuals. Disposal of the whole herd is therefore recommended where practicable. n alternative plan which has proved practicable is to regard the whole herd as an infected unit t to use the non-infected members to provide clean offspring which are weaned and tested at weeks of age and reared in isolation to form a new herd.

In the case of *Br. melitensis* in goats and sheep, immediate steps to eliminate the infection are viously desirable in any newly infected area, and elsewhere when practicable, but unfortunately ese desiderata are extremely difficult to carry out in many of the endemic areas. Sanitary measures prevent spread of infection from animal to animal and animal to man are therefore of the greatest portance but, again, may not be easy to put into practice. Vaccination with S.19 has been tried brucellosis in goats due to *Br. melitensis* but has not proved of value. Some encouraging results ve been obtained with certain other vaccines.

To sum up on methods of control I cannot do better than quote from the report of the Joint AO/WHO Expert Panel on Brucellosis (1951*b*):

"Conditions existing in the different countries of the world vary so much that the universal use of any one chnique or procedure for solving the brucellosis problem is impossible. The panel realizes that it will be ry difficult to inaugurate active programmes in some areas and countries; but the panel believes very strongly at such control measures as can be put into practice should be adopted immediately. The complete elimination brucellosis from herds, cattle, and countries should be the final goal."

Methods of Diagnosis

The tube serum agglutination reaction is generally regarded as the most practicable serological test oth in man and animals. The wide variation which exists in the methods and antigens used in ifferent laboratories and countries is, however, now recognized and, following steps already taken y the Office International des Epizooties (OIE) to standardize the test for bovines the Pan-American anitary Bureau and the FAO/WHO Panel have now adopted the OIE standard dried serum as an nternational standard for other species. The titres recommended as positive for bovine brucellosis re now defined in terms of this standard serum, viz. "the minimum positive titre should be 1/10 and 1/2 of the titre obtained when the standard serum is tested with the antigen and by the methods of he country concerned". It has now been recommended that workers on brucellosis in man and in nimals other than bovines, should seek to establish diagnostic criteria based on the same standard erum.

The rapid or plate test is regarded as an adequate substitute for the tube test, but it is usually ecommended that it should be adjusted to correspond to the tube test.

The complement-fixation test is used in a few countries and provides results which are usually omparable with those of the agglutination test, but it is not more accurate and is subject to greater ossibilities of technical error.

The opsono-cytophagic (*bacteriotropic*) *test* has special uses but does not appear suitable for routine se in animals or man.

The intradermal test has given rise to much difference of opinion, and many methods and antigens ave been used. It undoubtedly shows up a state of allergy, but whether this has any other diagnostic ignificance is questioned. Further planned observations are needed.

The ring test is a valuable screening method to locate infected herds especially in areas of low infection where much blood testing can be avoided. Its use has assisted greatly in eradication work in Denmark, Sweden and the United States of America. Further work is, however, needed on its value in vaccinated herds, especially where this has been done after calfhood. The test is essentially one for agglutinins in milk, which clump the stained bacteria, which are then brought up by the fat globules to produce a coloured cream ring.

Blood cultures are a valuable method of diagnosis regularly used for human cases, and great improvements have been made in recent years in both media and methods. It is agreed, however, that repeated attempts at culture should be made.

Other diagnostic methods used in animals include bacteriological and biological examinations of foetal or placental material or of milk, and microscopic and complement-fixation tests with placental material.

There is much other recent work that is of great importance such as that on smooth selecting factor (Braun, 1950) and on blocking and incomplete antibodies and on bactericidins, but no further reference can be made here.

Treatment

Although it has been shown that Aureomycin and chloramphenicol (Chloromycetin) are of value in brucellosis in animals and Terramycin may be expected to be, cost prevents their use except in a minority of valuable animals and for all practical purposes it may be said that the treatment of infected animals is not desirable.

Many advances have been made in recent years in the therapy of human infections, but it is not possible to deal with these here. Readers are referred to the FAO/WHO Expert Panel's Report and to the publications of Castañeda, Spink, Harris and Dalrymple-Champneys.

To conclude, Huddleson in his classical monograph quotes Charles Nicolle as saying:

"Mediterranean (undulant) fever is in the course of evolution and is tending to become chronic. It is a malady which, on account of its manifestations and chronicity, will become one of the most common and stubbornest diseases. . . . Mediterranean fever is a disease of the future."

Dalrymple-Champneys in his Milroy lectures entitled it:

"A neglected problem" and asked "Are we so very sure that undulant fever is a rare disease?"

Brucellosis certainly causes great loss in animals and much sickness in humans, and in many countries it is a major public health problem. Its removal is essentially dependent on control of the disease in animals and, like Castañeda, I would like to conclude by quoting the distinguished veterinarian who is Head of the United States Bureau of Animal Industry, Dr. B. T. Simms, when he said in the Symposium on Brucellosis (1950) held in that country in 1949:

"The future will bring eradication of brucellosis from our cattle herds as surely as the past has brought eradication of tick fever and tuberculosis. How far in the future this will be depends upon the energy, the perseverance, the knowledge of basic facts, and the whole-hearted co-operation of all of us who are interested in the prosperity and the health of our people."

Porcine, caprine and ovine brucellosis must be made to take the same journey. Economic and educational obstacles may hinder this end but total eradication of all brucella infection must remain our ultimate goal.

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Section of Orthopædics

President—PHILIP WILES, M.S., F.R.C.S.

[*November* 6, 1951]

Secondary Carcinoma in Bone Treated by Dienœstrol.—R. H. METCALFE, M.D., M.Chir., F.R.C.S.

Mrs. I. G., aged 65.

History.—1944: Right radical mastectomy for carcinoma of right breast. 1947: First noticed small swelling on left forehead. Had no treatment of any kind.

20.3.51: Fell on stairs and sustained subtrochanteric fracture of right femur through secondary deposit (Fig. 1). Admitted to St. James' Hospital. Fracture treated by extension on Thomas's splint. The photograph (Fig. 2) shows condition and appearance of secondary growth involving left frontal bone on admission. X-ray (Fig. 3) clearly shows gross erosion of skull and superimposed shadow of tumour.

FIG. 1. 20.3.51

FIG. 6. 25.9.51

FIG. 3. 20.3.51

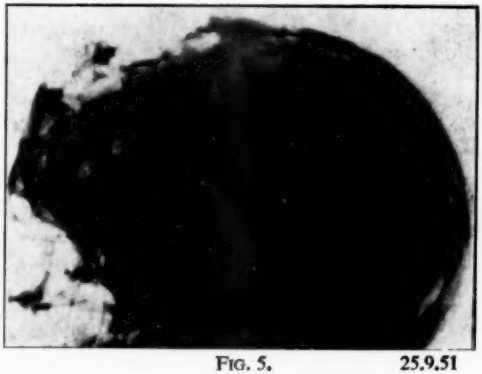

FIG. 5. 25.9.51

Patient treated by regular administrations of dienœstrol 5 mg., t.d.s. continuously up to present time. Tumour of skull greatly decreased in size and by July 31 was practically invisible on inspection. The condition at that time is shown in Fig. 4. Fig. 5, X-ray taken in September, shows further erosion of the bone of the front of the skull with disappearance of the superimposed tumour. Fig. 6, X-ray taken on 25.9.51, shows the fracture of the femur to be united and the secondary deposit to have disappeared.

1.11.51: Patient was up out of bed, walking slowly and had no neurological signs of any kind.

In answer to a question Mr. Metcalfe said that dienoestrol and stilbœstrol were both synthetic œstrogens (female hormones). The only difference was that dienœstrol was the stronger of the two and the dose required was therefore less.

FIG. 2. 20.3.51

FIG. 4. 31.7.51

POSTSCRIPT (December 1951).—She had had no special reactions to treatment such as bleeding or hirsuties. On the other hand, the treatment made her feel much better (in herself) and when it was stopped some two months ago it was recommenced at her own request within the week.

Subcapital Cuneiform Osteotomy of the Femur.—PHILIP H. NEWMAN, D.S.O., M.C., F.R.C.S.

Four patients who had had subcapital osteotomy of the femur performed for adolescent coxa vara were shown. This operation was preferred to the more distal type of osteotomy owing to the preferable anatomical position which resulted.

Three of these patients had maintained a full range of movement after the operation; the other starting with a good post-operative range of movement showed increasing stiffness so that a year after operation the joint had become ankylosed.

Case I.—V. G., female, aged 17. (Figs. 1 and 2.)

22.1.48: Admitted to hospital with history of pain in right hip and limp for three months. Symptoms first noticed while dancing but no other history of trauma.

11.2.48: Manipulation of hip attempted but no improvement in the position obtained. Skin traction of the leg was continued but there was still no improvement in position.

FIG. 1.—Case I. Before cuneiform osteotomy (lateral view).

FIG. 2.—Case I. Four years after cuneiform osteotomy.

15.2.48: Subcapital cuneiform osteotomy neck of right femur. Fixed with Smith-Petersen pin. Internal rotation plaster boot applied. After-treatment consisted of non-weight-bearing exercises both in bed and in the swimming pool.
10.6.48: Patient allowed up on crutches.
1.7.48: Patient allowed to weight-bear.
6.11.51: Condition of hip good—full range of movement.

FIG. 3.—Case II. One year after osteotomy showing decrease of joint space.

Case II.—F. O., female, aged 13. (Fig. 3.)

21.2.50: Patient's weight had been increasing for the past two years. Had complained of pain in the right knee and limp for two months.

17.3.50: Admitted to hospital. Some limitation of internal rotation, adduction and abduction of the right hip. Skin traction applied with no improvement.

27.3.50: Subcapital cuneiform osteotomy neck of right femur. Fixation by stainless steel screw. Plaster boot in internal rotation.

19.4.50: Exercises in bed.

21.6.50: Weight-bearing allowed (it has since been considered that this was too rapid progress at three months after the operation). The range of movement at the hip was at this time, flexion 90°, abduction 55°, adduction 20°, internal rotation 30° and external rotation 30°. Subsequently, when weight-bearing was allowed, the range of movement gradually decreased.

19.12.50: There was flexion 70°, abduction 20°, adduction 20°, internal rotation 10° and external rotation 10°.

4.9.51: When the patient was seen on this date the hip had become almost completely stiff and it was decided to readmit her to hospital for arthroplasty.

17.9.51: Metal cup and fixed-pin type arthroplasty performed.

6.11.51: Full range of movement at the hip-joint.

Case III.—A. W., female, aged 13. (*Not illustrated.*)

1.6.51: Admitted to hospital with history of limping for two months. Six weeks previously had hurt left hip but had little pain. Range of movement on admission was flexion 45°, abduction 20°, internal rotation nil and external rotation 40°–80°. Traction applied.

11.6.51: Subcapital cuneiform osteotomy performed. Hip spica applied.

11.7.51: Hip spica removed and exercises in bed commenced.

5.9.51: Range of movement was flexion 110°, abduction full, internal rotation 5°, external rotation 75° and extension 20°.

19.10.51: Walking with sticks. Range of movement full.

FIG. 4.

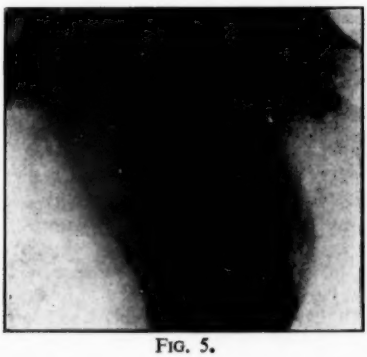

FIG. 5.

FIG. 4 (antero-posterior) and FIG. 5 (lateral view.—Case IV. Before cuneiform osteotomy.

Case IV.—D. L., female, aged 14. (Figs. 4, 5, and 6.)

15.2.51: Admitted to hospital with history of onset of slight pain in the upper part of the right thigh two years ago. Considerable weight had been gained during the past two years. Range of movement at time of

admission, flexion 10°, extension nil, abduction 20°, adduction 10°, internal rotation nil and external rotation 45°. Skin traction in bed for two months produced slight improvement of the position of the epiphysis, and later it was thought that it had again slipped back.

2.4.51: Subcapital cuneiform osteotomy performed. Hip spica applied in abduction and internal rotation.

9.5.51: Hip spica removed and exercises commenced in bed.

14.8.51: Patient allowed to walk. Range of movement, flexion 100°, adduction 20°, abduction 30°, internal rotation 20° and external rotation 30°.

6.11.51: Condition of hip good—range of movement practically full.

FIG. 6.—Case IV. Nine months after cuneiform osteotomy.

It was stressed that this operation was only indicated in those patients in whom the degree of slip was serious enough to be likely to interfere with the future function of the hip. This degree of deformity due to slipping of the epiphysis had been estimated as a third of the distance of the diameter of the neck and was estimated apart from the additional deformity produced by the bending of the metaphysis.

Operative technique.—Points in the operative technique were stressed:

An anterior incision was made with slight extension along the iliac crest. The rectus muscle was detached from its origin, the capsule exposed and a cruciate incision made in its anterior surface. This revealed a bluish-grey area of exposed metaphysis. This area gave an indication of the size of the base of the wedge of bone to be removed. The wedge of bone was cut with a curved osteotome and great care was taken when the edge of this instrument reached the posterior and inferior aspect of the metaphysis because it was at this point where most of the important blood vessels passed to the head of the femur. It was advisable if necessary to take out this wedge piecemeal rather than to attempt to remove it in one piece. After this wedge had been removed a hook was placed lightly into the undersurface of the epiphysis so as to anchor it while the limb was abducted and internally rotated. In this corrected position the epiphysis was generally found to be fairly stable on the metaphysis and it had been considered that fixation with a long screw or one pin of the Moore type was sufficient. The Smith-Petersen pin was possibly unnecessarily large and the difficulty, sometimes experienced, of driving it into the epiphysis produced excessive trauma. The operation was followed by immobilization for one month, by active non-weight-bearing exercises for a further three months. Weight-bearing was allowed after the fourth month.

Sometimes these patients presented themselves for operation after prolonged rest in bed and the affected hip-joint had become stiff due to traction and immobilization and the blood flow in the limb diminished by inactivity. It was necessary, for this reason, to give a pre-operative course of non-weight-bearing exercises, massage and even local heat treatment.

Mr. R. Glyn Thomas (Queen Mary's Hospital, Carshalton) said he did not follow quite the same practice as Mr. Newman. He personally used the Watson-Jones lateral incision. He had a little plasticine model made just before he did the operation and he actually carried out osteotomy on the plasticine model to get the correct plane of cut. He did a straight osteotomy—not a wedge osteotomy—and levered the head up. He did not let the patient out until after three months at least. The last case of this kind which he had treated had been very satisfactory.

Plastic Replacement of Femoral Head. (Six Cases) Second Report.—ST. J. D. BUXTON, F.R.C.S.

Mr. Buxton, in showing 6 cases, referred to the remarks he made on November 7, 1950 (*Proc. R. Soc. Med.*, **44**, 465). Although it had not been possible to present to-day all the cases he had shown a year ago, he reported that those patients were satisfied.

Of that series, Case 5 was shown and fourteen months after the operation was able to get on and off buses. J. B. had his operation eleven months ago and can ride a bicycle five miles, get on and off a bus, but finds uphill walking tiring. G. B. had his operation thirteen months ago and is at work in a soap factory. He can walk any distance and ride a bicycle.

As the operation has been employed for nearly two years in this country, experience is growing as to the indications and complications that arise. A communication regarding the latter will be made in due course. In Mr. Buxton's clinic there are a few cases of post-operative dislocation, myositis ossificans and one fracture of the stem of the prosthesis.

Section of the History of Medicine

President—LILIAN LINDSAY, C.B.E., LL.D.Ed., L.D.S.Ed., M.D.S. U.Durh., F.D.S., H.D.D. R.C.S.Ed.

(*November* 7, 1951)

Observations on Primitive Medicine, with Special Reference to Native African Medicine

By DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed.
[Edinburgh]

I HAD never been in Africa before 1951. I had surveyed mankind in China and also in Peru, but Africa remained the Dark Continent, strange and mysterious, waiting to be visited.

One might find something new there, for did not Pliny tell us many centuries ago that there was "always something new out of Africa"? Certainly so far as actual exploration went, the nineteenth century produced a succession of geographical thrills, and new features were added to the map at home as they were revealed in Africa by Speke and Baker, Mungo Park, David Livingstone and a host of others. There had been a time when cartographers added fictions of their own to fill the gaps—a whole series of lakes on the site of Lake Victoria, and of course the Mountains of the Moon, sometimes shown as a great range, extending right across the continent. But now, there was no need to draw upon the imagination, and gradually the blank spaces became filled and the field for further exploration became narrowed.

More recently the interest in Africa has become political and educational, rather than geographical, and has centred in the problem of a rapildy developing civilization and of how this may best be guided.

Sometimes I am asked what impressed me most during my African journey. Was it the native life or the big game, the strange exotic birds and flowers, or those gigantic physical features the Victoria Falls, the Great Rift Valley or the seemingly endless River Nile which I followed along its entire course? Those impressions were doubtless vivid, but Africa gave one something more, something moving and appealing, something almost spiritual, intangible and difficult to express in words, a sort of soulfulness which made one feel transported into another world. It hardly existed in South Africa or Rhodesia, but one began to sense it in Kenya and its spell became stronger in Uganda and still stronger in the Sudan. It was weird and uncanny, but in no way terrifying. It was, in fact, quite friendly and helpful, the sort of feeling which comes to those who are receptive when they visit lonely places, even in Scotland, such as the Hebrides. The whole background of Africa is conducive to strange happenings; one is not surprised to find it a land of magic and of witchcraft. I welcomed the mental process which made me so conscious of the supernatural in Africa. One of the main objects of my tour was to acquire some information regarding native African medicine. I was in quest of the witch-doctor. As might be expected, the investigation of witchcraft is a slow and laborious task, which demands not only time and patience, but also considerable knowledge of anthropology and of psychology.

Africa offered an attractive field for further investigation, although it was obvious that only after years of study could one speak with any degree of authority.

My information was acquired mainly at second hand, from natives or, as we ought to call them, Africans, some of whom had been patients, from African medical assistants in hospitals, from European doctors and anthropologists, and especially from missionaries, and from a perusal of the rather scanty literature on the subject.

The terminology is rather confusing—the so-called *witch-doctor* or, to use a better term, the medicine man, is not a charlatan. At least, he has an honest belief in his own powers, and the mere fact that when he falls ill he submits to treatment by another witch-doctor is evidence of his sincerity. The witch-doctor is not a witch; he is rather the enemy of the witch, the person who seeks out the bewitching agency in order to remove it. It is better to call him *medicine man* so as to avoid confusion, especially in this discussion which deals only with his healing function. The word *sorcerer* is usually applied to a malevolent person who causes disease rather than cures it.

Again, the word *medicine*, to the African, means much more than a drug. It is applied to any beneficial influence, just as the witch-doctor himself is not merely a healer of disease but one who can make rain in season of drought, can impute guilt to some individual, can recover lost or stolen property, and so on. Obviously his art is largely psychical: it is often termed magico-religious. But the two words should be differentiated, *magic* being a power which may be controlled by man, while *religion* implies control by a Power higher than man. Magic is a word which suggests trickery or deception, but when applied to primitive medicine it is an attitude or mental process which need involve no wilful deceit.

With those definitions clearly in mind, we may now proceed to view with a critical eye the problem of African witchcraft as applied to medicine, remembering that the primitive mind admits no such fine distinctions. To the African, medicine, magic and religion are all of a piece.

There was a time, not so very long ago, when even anthropologists regarded the so-called witch-doctor as a swindler, and his work as completely fraudulent. But a close study of the primitive mind has shown that primitive man's beliefs are genuine and are worthy of attention. Out of such a study there may emerge certain deductions which may be usefully applied in modern scientific medicine.

Witchcraft has played a sorry part in European history and it is still a malevolent influence in Africa and elsewhere. But there is another side to the picture. We cannot hope to assist the African in his struggle for a place in modern society unless we understand his ways, however peculiar they may seem. Primitive thought may seem illogical to our way of thinking, but primitive man does not reason as we do. He does not think in the abstract. In his mind, his dreams, his shadow, and the echo of his voice are realities, a part of his real existence which he does not seek to explain as physical or psychical phenomena. What, then, is his attitude towards disease, upon which he has founded his own peculiar system of medicine?

Disease is more ancient than man. Evidence of disease has been found in dinosaurs and other forms of life which antedated man by millions of years. Then when man arrived on the scene, disease was waiting to meet him and constituted one of his earliest problems as soon as he became able to think at all. He observed that animals ate certain grasses and plants when they were ill and he proceeded to do the same. Then by trial and error he discovered that some plants were foods, others were drugs (such as purgatives), others, poisons. His experiments dealt mainly with the vegetable world, and the majority of his remedies were derived from plants. All this was perfectly rational, and to this day we use some domestic medicines which our early ancestors discovered. Folk-medicine is probably the most ancient form of medicine.

But this did not explain *why* diseases attacked man. Thus the search for causes began and inaugurated a very different attitude towards disease. So it came about that primitive man came to regard disease as a supernatural phenomenon, to be treated by supernatural means. What more obvious than to suppose that those evils were the work of an enemy or the vengeance of an offended spirit. Animism is universal among primitives; it dominates all thought. Even to-day primitive man requires no Descartes to separate body and soul. For him they are one entity. He follows Plato in believing that the body cannot be treated apart from the soul, and vice versa. There is no separation between medicine and religion. The medicine man is priest, as well as physician, and the means of communication with the supernatural. But there is an important exception to this primitive attitude. Not all diseases are supernatural. The common diseases, such as malaria and the common cold, are not so regarded. In fact they are not regarded as diseases at all. They just come. As an old Bantu said to a friend of mine: "Those troubles are always with us and we cannot avoid them any more than we can avoid getting into debt."

And so it comes about that Africans and other primitive people treat their minor maladies by domestic remedies just as we do. We do not call in a doctor for a cold or a headache or slight digestive upset. We take an aspirin, just as our grandfathers took senna tea or liquorice root. The African is also his own doctor up to a point, and there are some who have developed their herbal knowledge still more and who practise as herbalists in a logical fashion.

Thus, there is a sort of gradation in medical treatment. Trivial affections are treated by the patient or his family, or, if need be, by a herbalist. But if those remedies fail or if the disease is obviously serious, the assistance of the medicine man is invoked. He proceeds with his diagnosis, not in order to give the disease a name and apply appropriate treatment, but in order to ascertain its cause and remove it. Diagnosis and treatment are as one. The method is based upon the belief that something has entered the patient's body, or, something has been extracted from the patient's body. The intruder may be an evil spirit which has entered the body under its own power, or has been projected into the body by some other evil spirit, by an enemy, by a dead person, or by an animal. Or there may be a material intrusion—a dart, a miniature arrow, a crystal of quartz, a stone, an animal (most frequently a worm). This idea of some simple particle projected into the body and causing disease is an ancient belief which is really quite rational. Many diseases are caused by bacteria and even to-day we do not know how many organisms gain entrance. Disease then, to the primitive mind, may be caused by the entry into the body of demons or darts, spirits or stones, things spiritual or things material. Those may be combined, the stone or dart is believed to contain the spirit or demon. In Africa the spirit is more often the culprit than is the material object.

Disease may also result from the abstraction of something from the body, and that something is usually the soul. It is commonly believed that the soul leaves the body during sleep, during a fainting attack, and during many forms of illness. Unless it can be induced to return, the patient dies. Again, the soul may be lost or mislaid, or even stolen or eaten by witches, and it is the business of the medicine man to seek it out and induce it to return. This idea is very widespread among primitives.

Less frequently, disease is attributed to the abstraction of actual tissue from the body, such as blood or fat, or even some vital organ such as the heart or liver. This belief is more often found in Australia and the South Seas than in Africa. Those various ideas may be intermingled; for example, the loss of the soul may leave the way clear for a demon to enter the body, or to leave room for the entrance of the foreign object carrying the disease. This is a common African belief.

In general it may be said that the entry of a material object causes pain or swelling in some part, while entry of a spirit causes more general illness, such as fever. Diseases associated with fainting or unconsciousness are thought to arise from loss of soul.

In treatment, drugs play but a small part, and anyone who sets out to study the native medicine of Africa will soon discover that he is following two routes of investigation. The first, which lends itself to scientific research, concerns the values of plant and animal remedies, and certain physical methods of treatment such as massage and baths. The second, which demands some knowledge of anthropology and psychology for its study, is concerned with supernatural means of cure and is not nearly so easy to study.

The materia medica of primitive man has already supplied useful knowledge to medical science. Opium, cocaine, quinine, digitalis, and other remedies were originally used in empiric fashion by primitive people. But since the discovery of synthetic drugs this field of research is greatly contracted and few pharmacologists are interested in it.

Most of the drugs are derived from plants, but lower forms of plant life, fungi, mosses and ferns are seldom used. It is from the highly differentiated plants that the remedies come; and, in Africa, the roots and leaves are the parts most often used. The juices, wood, stems and seeds are less frequently employed. The plant may be eaten raw, but more frequently it is prepared as an infusion or decoction. The dosage is very uncertain.

Animal substances such as blood, fat, milk, horn scrapings, are not so often used, nor are such mineral substances as iron ore, salt, and mineral waters.

Dr. Leakey, whose work in archæology is well known, told me that zebra fat was widely used in Tanganyika as a remedy for tuberculosis, and that he was convinced that it was of value, although he had never been able to persuade anyone to test its value in a scientific manner. It is the subcutaneous fat alone which is used—a substance of creamy consistency like thick oil.

Many plant remedies have been studied. Professor Watt of Johannesburg has reported upon over 1,500 species, the majority of which were found to be inert. Dr. Scott of Nairobi told me of investigation of the African arrow poison prepared from Acocanthera, which I saw growing in his garden. The Agricultural Officer at Kabale, Mr. Purseglove, showed me his notes on over a thousand plants alleged to have medicinal properties. He said that the native names of the plants were by no means reliable and one name might be applied to several plants of different species. He also mentioned that a large number of the active plant remedies were purgatives. On the whole, it seems very doubtful whether any further discoveries may be expected from this line of research.

Another interesting field of study is to be found in the various physical modes of treatment used by primitive people. The vapour bath or steam bath is widely used, chiefly for rheumatic pains, but also for fevers and a variety of ailments. David Livingstone describes how he tried this remedy but remained unconvinced of its efficiency.

Massage is a universal remedy. Sometimes the feet are used instead of the hands, as the instruments of massage. The stroking is often towards the extremities, with the idea of expelling the disease, and it is doubtful whether massage and vapour baths were mere empiric remedies or whether they originated in the attempt to get rid of the evil spirit or material intrusion.

Cupping is commonly used in Africa where the horn of an animal, perforated at the tip, is the instrument through which suction is applied, the opening being then closed by a piece of wax. Suction is largely used in Australia but without any cup or instrument, as there are no indigenous horned animals.

Surgery is, of course, in a category of its own, and it is sometimes said that surgery is older than medicine. That may be true, if the remark applies to the treatment of wounds and fractures. Operative surgery could not develop until anatomy had been studied, a notable exception being the operation of trephining which originated probably to allow the exit of a demon from the head and which is still practised in Algeria and Somaliland but nowhere else in Africa. The age-long association of surgery with barbers and blacksmiths is curious; they were doubtless the only persons who possessed the tools. Not so long ago many Scottish blacksmiths were also bone-setters, and in Africa the medicine man is frequently also a smith.

But those drug remedies and physical remedies are quite a subsidiary part of the medicine man's treatment. The use of such remedies no doubt enhances the prestige of the healer and it seems probable that in Africa as in Europe the patient feels more confidence in the doctor who follows an active line of treatment and does not merely watch and wait upon Nature. The fundamental basis of witch-doctoring is an attempt to control the supernatural, to seek out the witch, to dispel the intruder causing the disease, to induce the soul to return to the body. It would be useless to attempt any general description of the means employed, as these vary so enormously in different parts of Africa and few of them have been studied by expert anthropologists. They involve the use of songs and incantations, of dances and contortions and of many strange magical rites. As a preliminary step the medicine man may induce in himself a state of trance, or may work himself into a frenzy of excitement. Music, strange costumes or masks, dancing and antics all have their part in heightening emotion and acting as a means of suggestion. One of the most extensive local studies has been made by Evans Pritchard among the Agande people of the Southern Sudan.

A common method of investigating disease in Africa is that of divination by throwing into the air a number of bones or sticks and noting the pattern which they assume as they fall to the ground. By this means the Bantu and other Africans claim that they can determine the cause of the disease. Very often there is also a careful and searching questioning of the patient, so as to ascertain his social environment, his domestic relationships, his worries and troubles. This would seem to be sound psychology, as we now know that diseases such as gastric and duodenal ulcer may be the result of such emotions as anxiety or fear. Thus it would appear that the medicine man is the counterpart of the psychoanalyst. The confession of some sin or antisocial act may be the first step towards cure—a cure of soul and body at one and the same time. This attempt to ascertain the relationship between the disease and the daily life of the patient is a part of what we now call Social Medicine.

Other methods employed by the medicine man include the transference of disease to animals, on the scapegoat principle. Indeed, the goat is most frequently used for this purpose, although in some places a double transference is undertaken. The disease is first induced to enter a goat, then transferred to some useless animal, such as a frog, which is then killed.

From what has been said it will be obvious that there is some rational basis for the methods of the so-called witch-doctor of Africa. Modern medicine may even glean some useful hints from a study of the primitive healer. But more important still, especially in Africa to-day, is the reaction of witchcraft to the impact of a rapidly advancing civilization. The Witchcraft Suppression Ordinance of 1896 stamped the witch-doctor as a criminal, and drove his practice underground, so that even to-day it is not easy to ascertain who is the medicine man and to what extent he is consulted. It is quite certain that legislation has not abolished witchcraft, and the fact is now so fully recognized that persons suspected of its practice are treated leniently. Education would seem to offer a better means of dealing with the evil.

But the problem is far from simple; *homo sapiens* finds it very difficult to understand *homo divinans*. The African of to-day is eagerly grasping at the civilization which the European forecasts. He is trying to secure within one generation what Europeans have taken centuries to acquire. He is ceasing to till the land and is flocking to the towns. And who can affirm that he is any happier? Who will argue that what is best for us is also best for the African? Several Africans with whom I spoke had experienced a great disillusionment as a result of the two wars. They were sorely puzzled and hardly knew what to think. Although they still look to Europe for leadership they are unwilling to jettison their old beliefs. We cannot help them in medicine, in law, in education, or in any other activity, unless we realize the nature of their background and the framework of their basic beliefs. That is why a study of native African medicine is so important. It is not merely a study of the obsolete, the magical, and the curious, but rather a study of the foundations upon which a modern Africa will be built.

[*December* 5, 1951]

Folk-Lore and History in Veterinary Medicine [*Summary*]

By L. F. Newman, M.A., F.R.I.C., F.S.A., Dip. Agri. (Camb.)

The last fifty years have seen a great increase of interest in the history of medicine, but medical history, that is the bearing of disease, sudden death or accident on the course of world events, especially in the case of the more intimate details, has been neglected in recent years and the folk-lore of medicine has never received much attention.

Veterinary folk-lore and history are intimately connected and can only be considered as one subject. The status of the full-time professional farrier or horse-doctor and of the irregular veterinarian was largely a matter of local reputation. The very wide term "farrier" was often used in a dyslogistic sense and T. L. Peacock in his musical farce *The Three Doctors* (written about 1810) emphasizes this, for his characters—the pompous little M.D. and the self-assertive member of the new Veterinary College, always on the defensive—were probably drawn from life, but Peacock entertained a very strong prejudice against the medical profession and, presumably, against veterinary surgeons as well.

An exact definition of the term "folk-medicine" is difficult. In Anglo-Saxon times the remedies employed by the regular physician, the local wise woman or white witch, the farrier and the horse-leech were all similar in character; Payne (1904) quotes a large number of charms, incantations and many common remedies. Warren Dawson who edited a leech book of the fifteenth century (1934) comments on the fact that out of more than a thousand prescriptions only about half a dozen related to veterinary medicine but it may well be that the compiler was a physician, and did not recognize equine or cattle practice.

The rise of the universities with medical schools conferring a tangible qualification created a real distinction between the physician and the village folk-healers so that four well-marked types of practitioners developed: (1) the dignified physician, (2) the surgeon, (3) the apothecary with a good working knowledge of pharmacy and of everyday disease, and (4) the village wise woman or white witch, the simpler and the various grades of unqualified empirics. With this fourth class may be included ladies of the castles and manor houses who treated their local villagers and dependants without fee and who possessed the means to provide medicine, food and dressings. The great convents and monasteries also cared for the sick and injured.

The position of early veterinary medicine was very different. The care of animals, especially of horses, was a matter of the greatest interest to all classes in the pre-mechanical ages of transport. There was no exact equivalent to the physicians but the farrier—originally a surgeon—and the horse-leech, were important members of the rural population. Specialization seems to have started very early in time. The laws of Hammurabi who was a contemporary of Abraham (2285–2242 B.C.) differentiated between cow doctors and sheep doctors, and down to the end of the eighteenth century there appear to have been specialists for each species of farm animal.

Before railways covered the countryside horses were the only means of transport. The poorer classes walked from place to place and farmers used the slow but cheap draught ox, an animal whose upkeep was only a fraction of that of the more expensive horse. But everyone who could travelled on horseback. Elderly persons and nervous ladies were carried in litters or cumbersome coaches while others rode pillion. The nobles and ecclesiastics who travelled with extensive retinues kept a large number of horses for sport and travel and everyone who could afford it had a stable proportionate to his social position. During the Commonwealth the

stage-coach system was established and the large inns maintained teams of horses for each stage and, later on, for post-chaise, and posting relays. Road wagons conveyed goods from town to town and required teams of 6 or 8 heavy horses, and before their period pack-ponies were required in great numbers for freight transport. Equine diseases were carried from stable to stable and sanitary conditions were deplorable. Cuts, wounds, spur marks and other injuries incidental to travel invited infection so that the medical and surgical care of horses was of great importance and every gentleman, farmer and villager was more or less skilled in the veterinary practice of his times. The squire and the small farmers called in the bullock-leech, the horse-leech, the sheep doctor or the gypsy to attend to farm animals in cases beyond their own powers of treatment.

Sudden and widespread epidemics were common apparently after wet seasons. The *Anglo-Saxon Chronicle* refers to several such outbreaks and the seventeenth century "Essex murrain" still lingers in folk-memory. Pliny records epidemics of the murrain in Gaul, and in the year 684 an animal plague raged through Europe for three years and destroyed nearly all the farm animals. Sheep diseases are first mentioned (in England) in the thirteenth century. There was a "great sheep rot" in 1238 and scab is mentioned in 1288 (Seebohm, 1927).

Jean de la Ruelle (physician to Francis I) published his great work *Veterinariæ Medicinæ* in 1530 and Snape's *Anatomy of the Horse* appeared in 1683. These books probably exercised a greater effect on veterinary science than any other works. Vegetius' *Ars Veterinaria* was published at Basel in 1528.

It may be said that, in the past, the physician was a man of good social position while the village simplers and healers were mostly illiterate peasants. In veterinary medicine the position was reversed, the nobles and gentry were skilled amateur practitioners while the professional veterinarians of all grades and types were drawn from the lower classes or were wandering illiterate gypsies. The "sow gelders", for example, appear to have been extremely competent and skilful. Garrison (1917, 2nd ed.) quotes two cases: In 1500 Jacob Nufer delivered his wife by Cæsarian section, while another gelder, a little later, was said to have successfully performed a double ovariotomy on his daughter. But right down to the present century the most important class of irregular horse-doctors were the wandering gypsies. This nomadic race retained some ancient lore of herbal and other unorthodox cures, now lost for ever, and they were born "horse handlers". They claimed—or some of them did—to have the secret of "The Whisper", and they knew all the ways of the copers and fakers. The law of market overt gave the horse coper an excellent chance of showing his abilities. Broken-winded horses were given a dose of small shot in oil before they entered the sale ring while sluggish animals were made to swallow a small live eel. A piece of chewed ginger in the rectum had a similar effect, and readers of Surtees will remember Mr. Jorrocks' dream. Bishoping—filing and blackening the teeth—to make the horse appear younger than it was, was easy to detect but a nail driven into the *sound* foot of a lame horse so that the animal was equally lame on both feet was a difficult operation and not easy to detect in a crowded show ring. The practice of "unnerving", that is the removal of an inch or so of nerve from the leg of a lame horse to prevent any feeling in the foot until regeneration took place, was highly dangerous as the horse was liable to stumble on rough ground and the operation is illegal. Irregular horse-doctors had appropriate cures for many common equine vices. Horses who threw themselves on the ground had their feet secured together with hobbles and were left where they were for twenty-four hours; the trick of rearing when the rider mounted was cured by tying the horse head and tail across a doorway and allowing boys to jump over its back for hours at a time. Horses who refused to start (a not uncommon vice) were stimulated by a straw fire lit under their bellies, while the backing habit was cured by a few nails driven into the harness. None of these cures was considered cruel as the horse could obtain instant relief by good conduct.

Farm horse-keepers used simples to improve their charges' condition. Dog's mercury was dried and the powder scattered over horses' food; arsenic rubbed on rags secured to the bits made carriage horses salivate and produced the "spume flakes" so greatly admired by the early Victorians. Scents were much employed to soothe animals; dogs, rats and pigeons are attracted by aniseed, while cats are fond of catmint and valerian. Coles (1656) writes of the former plant: "If you set it the catts will get it, if you sow it the catts can't know it". Up to a few years ago it was usual for dairy farmers to keep a billy-goat with their cows on the ground that the hircine smell of the goat prevented abortion in the herd.

It is said by dog stealers that when the warty growths on a horse's knees split and become damp before breaking off, dogs will follow anyone who carries a piece in the warm hand. Farm hands still come to rural druggists and ask in a shamefaced manner for oil of rhodium. About a year ago a Sunday newspaper had the story of a successful use of folk-treatment in the case of Sunstar when he won the Derby for his owner Mr. Jack Joel. Sunstar was pulled up lame after his last training gallop and his chance of winning was considered hopeless until his trainer, as a last desperate chance, wrapped the swollen leg in cabbage leaves—a very old folk remedy. The dried sweat of horses was once in great repute as a cure for drunkenness, and is said to be still used in South Africa.

The "horse-doctors" always began their examination by tasting the patient's urine for sugar, a procedure tha (substituting the use of Fehling's solution for taste) might, with advantage, be followed today. Dutch artists often painted physicians examining flasks of urine, presumably for sediments, but there is no evidence that they tested for sugars. Marlowe alludes to this in the scene (*Tragical History of Dr. Faustus* ed. 1604) where Faust has sold a horse, made by art magic, to a courser for 40 dollars: the courser says: "If my horse be sick or ill at ease, if I bring his water to you you'll tell me what it is?" Faustus: "Away you villain! What dost think I am, a horse doctor?"

The leech-books of the Anglo-Saxon doctors; the great "Herbals"; the works of county gentlemen or the better educated farmers with a taste for veterinary science contain many interesting examples of folk-medicine. Fitzherbert in his *Book of Husbandry* (1534) gives a number of cures for the diseases of farm animals but he had a very low opinion of veterinary practitioners: "A horse-mayster is he that bieth wylde horses or coltes and bredeth theym and selleth theym agayne wylde, or breaketh parte of theym and maketh theym tame and

then selleth them. A corser is he that byeth all rydden horses and selleth them agayne. The horse-leche is he that taketh vppon him to cure and mende all maner of diseases and sorsaunce that horses have. And when these three be mette if ye hadde a potycarye to make the fourthe, ye mighte have foure such that it were harde to trust the best of them. . . ."

Coles (1656) in his little book *The Art of Simpling* was the first of the herbalists to devote a section to veterinary simples and the chapter "For Bruit Beasts" contains a number of appropriate cures with some notes on toxicology. Coles' knowledge was academic and he was devoted to the doctrine of signatures. He quotes Mirzaldus on veterinary remedies and a few other early authors. Tusser had little to say on care of animals—he was not a stock farmer but he mentions a few remedies.

Reginald Scot (1584) quotes B. Googe (*see* ed. 1614) as giving details of treatment for farm stock. Scot also recommends Vegetius as an authority but adds that "unlearned men" should consult a "bullocke leech".

Stories of were-wolves, yales, vampires, and the problem of "cocks' eggs" which, if successfully incubated, hatched into basilisks, &c., belong to ordinary folk-lore rather than to veterinary science.

W. Ellis, a prolific writer of textbooks on agriculture (1750) was one of the first to deprecate the use of urine or manure-liquid as a medicine. These substances had been in great repute. At the present time cesspool liquid is much used for animal cures by amateurs and the irregular horse-doctors. Ellis assumed that "Warbles" were carried in dung-liquid and he was also an advocate for soot as a general remedy. Hartman, a friend of Sir Kenelm Digby, in his book *The Family Physitian* has a chapter on animal remedies and even to-day shoeing smiths grease nails or other foreign bodies that have caused injury to horses' feet and hide them away, leaving the wound to heal without treatment. But needless to say, they do not use the "powder of sympathy".

W. Gibson, a popular writer on veterinary medicine in the early part of the eighteenth century, was a well-educated farrier with a fair knowledge of the pharmacy of his time. He quotes largely from Mead and the Sieur de Solleysell. The latter author was "Querry to the French King for his great horses" and a European authority on veterinary medicine; his book *The Compleat Horseman* was published in English in 1696. He laid great stress on the markings of horses.

G. Markham was the first to include a chapter on training horses for racing and his "Master-Piece" (1734, 21st impression) was very popular.

Human medicine is as old as human origins, but the veterinary art only dates from the patriarchal period of the domestication of farm animals.

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JOINT MEETING No. 1

Section of Pædiatrics with Section of Obstetrics and Gynæcology

Chairman—Professor A. G. WATKINS, F.R.C.P., M.D.
(President of the Section of Pædiatrics)

[*October* 26, 1951]

DISCUSSION ON THE CARE OF THE NEW-BORN BABY

Professor A. G. Watkins: I wish to describe some of the methods we have been using in Cardiff in the care of the new-born baby at St. David's Hospital. This is an old Poor Law Hospital whose buildings by modern standards are completely old-fashioned but modifications and adaptations have allowed us to have a maternity department of just under 2,000 births a year with a unit of 25 cots for premature babies and a breast-milk bank.

The new-born babies and the premature unit are under the day-to-day care of a consultant pædiatrician and a sister who is in charge of all the babies with sisters for each section.

On receiving a baby from the labour ward after immediate resuscitation he is placed without clothing and without bathing into his cot. If soiled badly by meconium or blood this is gently removed but normally this is unnecessary. The baby is not bathed until the cord is off at the 6th to 8th day and this is first done in the presence of the mother who thereafter baths the baby herself until their discharge home.

The standard cot we use is of the Sorrento pattern and Dr. J. Jacobs has devised a simple means of converting it into an oxygen bed by covering it with two halves of a Perspex lid held down by a spring wire and hooked to the base of the cot. This device allows easy vision and access to the baby and an oxygen concentration of between 30 and 40% with a flow of 2½ litres per minute. This can be increased to 60 to 80% if needed.

The temperature of the nursery is kept at 70° F. (21° C.) and the cot temperature is increased by hot bottles which are guarded from the baby by a Perspex hood. The babies are kept in this oxygen bed for as long as their condition warrants it as judged by their colour, activity, cry, &c.

About three to four hours after birth the cord is cut short leaving a stump about ¾ to 1 in. long. This is sealed by pouring collodion over it and left without powder or binder until the stump drops off at the usual time. We have had no sepsis by this method and it does away with a great deal of unnecessary handling of the baby.

No eye drops are used prophylactically. The drops themselves are not always free from infection if the solution has been in stock for some time and the eye may get infected by the nurse's hands. Therapy of a sticky eye is so satisfactory that the old preventive routine with its reactionary conjunctivitis is no longer needed. The staphylococcus which is the commonest organism found in the eyes seems to be developing a resistance to penicillin at any rate *in vitro* but fortunately most of them are Aureomycin- or streptomycin-sensitive.

The babies are nursed naked except for a napkin and to watch their natural movements of limbs and chest shows what a deterrent clothing must be to lung expansion. We have been impressed in the study of the respiratory movements of the new-born babies with their remarkable irregularity in both depth and rhythm.

Thus every attempt has been made to leave the baby alone with a "no touch" technique with no binder, clothing or bathing and it is obvious that not only does this lessen the risk of infection but also reduces the nursing task tremendously. Deaths attributable to infection were 10 in 1948, 6 in 1949 and 3 in 1950.

No baby is fed until he shows evidence of hunger. This method was first used with the premature babies where it undoubtedly lessens the risk of aspiration of milk before a cough reflex has been established and we have found it of equal value in the full-term baby especially if there has been any respiratory or cerebral difficulty at birth. It is not easy to describe the hunger cry but sisters and nurses recognize it without difficulty. It is accompanied by restless movements and sucking the fist. Once the baby has achieved this, and it may take up to forty-eight hours, though the average is about thirty hours, he is given a first feed of saline to test the continuity of the alimentary tract and the cough reflex.

If all is well he is then taken out of the nursery clothed in a light gown only and given to his mother to feed. From then on so long as he remains healthy he stays with his mother in the ward. He is fed three-hourly but discretion with a night feed is encouraged if he cries with hunger. We are interested in trying a completely free demand schedule of feeding for comparison with this method but the shortage of nurses is one difficulty.

A criticism sometimes levelled at this technique is that the mother does not see her baby for twenty-four hours or more but this position is explained to the mothers who have accepted it as a custom of the hospital. It seems to us that the baby gets most of his crying over in the first few hours and he settles down more easily than if he is put direct to his mother.

The babies are placed in cots at the end of the mother's bed though we should prefer them alongside so that she can attend and see to her own baby. She thus gains confidence in handling her child and there is much less chance of her passing him on to granny when he goes home.

We have had no trouble with delayed feeding with engorged breasts perhaps partly due to antenatal care and it appears that colostrum is not so valuable to the human baby as was previously thought.

Every mother attending the antenatal clinic is encouraged to attend the special lactation clinic run by the pædiatric sister. We have no doubt of the value of Dr. H. K. Waller's antenatal expression of colostrum and wearing of Perspex nipple shields or shells. Since we have held this clinic not only have we a better rate of breast feeding but a much smoother establishment of lactation and far fewer breakdowns when the mothers go home. The troublesome and painful engorgement period has disappeared and the mothers are well conditioned to the idea of breast feeding when they come into hospital.

The lactation clinic is part of the set-up that supplies the breast milk bank, for its donors are made up from its attenders. These donors are selected while in hospital for their suitability both as to their capacity as milk yielders and their standard of personal hygiene as assessed by the sister in charge of the new-born. Donors are paid 2d. per oz. but they must be feeding their own baby satisfactorily as well. The milk is collected at their homes, pooled and pasteurized and distributed outside the hospital in ice-box containers and charged for at the rate of 6d. per ounce. About half the weekly collection of 250 pints is used by the hospital, mainly, of course, in the premature baby unit.

This is not the time or place to give details of the breast-milk bank but it should be stressed that it is part of the cycle of events that helps to build up a maternity service. In the premature unit provision is made for mothers to remain resident in the hospital until such time as their babies are able to suckle at the breast. This may mean a stay in hospital of many weeks but we have been able to obtain a satisfactorily high breast-feeding rate.

We have tried to work to the following principles:

(1) That each baby requires and should have as careful a medical examination and supervision as any other patient in a hospital.

(2) That the aim of a maternity hospital should be to capture the spirit of the home birth as nearly as institutional life will allow.

(3) That every effort should be made to promote and maintain breast feeding.

(4) That the routine of a hospital be such that the risk of infection is reduced to a minimum.

Fashions in neonatal care may change, but we are satisfied that with a sound strategy the tactics may well be varied considerably. That at least we have done no harm in the introduction of these methods is shown by the satisfactory drop in neonatal deaths of 33 per 1,000 live births in 1946 to 24 per 1,000 live births in 1950.

Dr. J. Jacobs showed and commented on the slides which illustrated Professor Watkins' account of the pædiatric work in the maternity unit.

Mr. J. B. Blaikley: In most people's experience staphylococci have, during the last ten years or more, come to take an increasingly prominent place in producing infections both of mothers and babies; during the same period infections with hæmolytic streptococci have almost disappeared.

During these years a number of hospitals have had serious epidemics of staphylococcal infections, sometimes the predominant lesion has been acute mastitis, at other times it has been pemphigus neonatorum. Furthermore, infections in the new-born baby such as conjunctivitis, septic rashes, and septic fingers are not uncommon, and are almost invariably due to staphylococci. New-born babies are, of course, peculiarly susceptible to this organism.

Our attention, at Guy's Hospital, was forcibly directed towards the staphylococci towards the end of 1941, when we had the first of a series of outbreaks of pemphigus. In all there were five definite epidemics in just over a year; each started suddenly and lasted about three weeks, and there were intervals clear of infection between whiles. At that time all obstetric patients were admitted to a single ward of 24 beds.

In March 1942 Dr. F. A. Knott, clinical pathologist to the hospital, with my help investigated the outbreaks and set to work to develop a preventive technique.

The first step was to try to sort out the staphylococci, and since everyone harbours staphylococci, to try to recognise in some way those responsible for the epidemics. Since it is not possible to group staphylococci as one can streptococci, Knott set to work to grade them according to their biochemical activity, which seemed to him to give a good indication of virulence, and he arbitrarily divided them into four grades, A, B, C and D. Table I shows the criteria of grading.

During the twelve months March 1942 to February 1943, there were 4 outbreaks; although each was terminated in turn, it was only at the expense of closing the ward with complete dislocation of the work of the department, and it seemed only too certain that further outbreaks could be expected.

It became apparent, however, that the staphylococci responsible for epidemics always fell into grades A or B, and as a result of our experience it was evident that the infection, while it might be introduced by someone with obvious clinical infection, was usually introduced by an attendant, who was a symptomless carrier, usually in the nose. Table II shows the incidence of the various infections and the grades of the staphylococci.

TABLE I

Grades	A	B	C	D
Pigment	+++	+++	++	+
Coagulase	++	++	±	∓
Hæmolysin	+++	+	±	∓
Gelatin	+	±	±	−
Mannite	A_{24}	A_{48}	A_{72}	A_{72} or −
Lactose	A_{24}	A_{24}	A_{48}	A_{72}
Sacchar.	A_{24}	A_{24}	A_{48}	A_{72}
Maltose	A_{24}	A_{24}	A_{48}	A_{48} or A_{72}
Glucose	A_{24}	A_{24}	A_{24}	A_{24} or A_{48}

All Grade A and B strains are considered invasive and exclusion of the patient or carrier follows.

TABLE II

Lesions	Staphylococcal grades A	B	C	D
Breast (abscess)	3	3	0	0
Breast (inflammation only)	3	9	5	1
Wound sepsis following C.S.	2	4	0	0
Pemphigus	15	14	2	0
Septic rash or boils	10	26	8	3
Septic finger	5	3	1	0
Conjunctivitis	2	16	6	1
Fifty consecutive "normal" but + skins in mothers	1	4	17	28

Tables I and II are reproduced by permission of the Editor of the *Journal of Obstetrics and Gynæcology of the British Empire*.

Only a very small proportion of *Staphylococcus aureus* falls into these two groups, and it becomes possible to exclude staff so infected, whereas, if all carriers of *Staphylococcus aureus* are to be excluded, it becomes very wasteful or in fact impossible owing to the large numbers involved. Further it is possible to spot the offending person in twenty-four hours if group A, or forty-eight hours if group B. Phage-typing which has been advocated to trace the origin of an epidemic, though certain, has the disadvantage that it takes four or five days, which is too slow if one is to check an epidemic before it gets going.

In March 1943 therefore we introduced a system of continuous bacteriological control which has been maintained ever since. (Up till this date all ordinary care had been maintained including the wearing of masks when handling babies.)

Our routine is to swab all nurses before commencing work in the department and at fortnightly intervals afterwards, all students before taking their turn of duty in the delivery room, also house-officers and other staff periodically. In addition swabs are taken of anyone who develops an infection of the upper respiratory tract. Swabs are ordinarily taken from the nose, throat, and hands.

Any nurse or student found to be a carrier is put off duty until clear as shown by negative swabs on two successive occasions.

Patients are similarly swabbed on admission, including one swab from the vagina. Any patient found to be a carrier is isolated.

Since it had become evident from swabbing articles in the ward, and from sampling dust, and sampling the air with the Bourdillon slit sampler, that articles handled may show pathogenic staphylococci not infrequently, but the air and ward dust almost never, great emphasis has been placed on washing the hands before and after handling any baby; the hands are washed under running water and dried on small sterile squares of waste linen.

To reduce the handling of babies and to avoid damage to the delicate cutis of their skins, bathing is kept to a minimum, namely, soon after birth, when the cord separates and afterwards at intervals of five days or so. Each day's supply of dusting powder, olive oil, &c., is sterilized before use in the bacteriological department.

Only fathers are allowed to see the babies and they wear masks. Babies are not allowed in the ward during visiting hours.

The diagram in the *Journal of Obstetrics and Gynæcology of the British Empire* (Blaikley and Knott, 1944) shows very well the differences between the two years; that preceding the introduction of full bacteriological control in March 1943, and that after. Although during the second year there was quite a steady incidence of carriers, their early exclusion, coupled with the careful observance of our other preventive measures, was most successful.

There were 225 confinements in the first year, and 375 in the second.

Up to date we have had no further epidemics in spite of the fact that the department is housed in two large wards of 23 beds each and two large nurseries. In March of this year there was a threat of trouble due to a lessening of care in the swabbing routine at a time when there was a higher incidence of carriers than usual, but a vigorous enforcement of our control immediately checked any spread of infection. At the same time there has been remarkably little sporadic infection in the babies, such as "sticky eyes". Grades C and D will give rise, we find, to sporadic cases of mild infection, but never to epidemics. Prior to an epidemic there is a noticeable increase in the number of swabs showing grades B and then A, and I believe February, March, April and May are months particularly liable

to be accompanied by outbreaks of staphylococcal infection. Perhaps lack of sunshine is a factor favouring the growth and increasing the virulence; it is certainly true that cultures are readily rendered sterile by sunlight.

Allison and Hobbs (1947) in the City Lodge Hospital, Cardiff, used phage-typing and identified a single strain of staphylococcus, or occasionally two, as being responsible for an epidemic. Knott used phages to confirm the origin of the responsible staphylococcus in our own investigations, and was able to prove the carriers found by his own method were, indeed, the source, but we found phage-typing too slow for clinical purposes. The only difficulty to my mind in the adoption of Knott's grading is the fact that there is no hard and fast line to be drawn between grades A and B, B and C, C and D. An over-anxious bacteriologist can up-grade the staphylococcus so that the carrier rate of so-called A and B grades is so high that it becomes impossible to exclude the affected staff. The method properly used never shows more than a 2 or 3% carrier rate and for months on end the rate is nil. The work involved is not great if a hospital has an established bacteriological department, and in my experience the absolute control of staphylococcal infection in Guy's Hospital maternity department has been of the greatest value, both directly to the mothers and babies, and indirectly in the avoidance of the closure of beds.

No reference has been made to Colebrook's work on infection of burns because this problem and ours are different. In a ward full of infected burns, there are millions of staphylococci in the bed-clothes and inevitably on the floor and in the dust. It is impossible to exclude infection. In a maternity unit, however, this is possible, and the dust and air are therefore seldom harbouring pathogenic staphylococci, and never should become a danger.

REFERENCES

ALLISON, V. D., and HOBBS, B. D. (1947) *Brit. med. J.* (ii), 1.
BLAIKLEY, J. B., and KNOTT, F. (1944) *J. Obstet. Gynæc.*, **51**, 386.

Professor G. I. Strachan was enthusiastic about the "no touch" technique and wished that it could be applied to the mothers too. He recalled an outbreak of mastitis in a maternity unit which was only checked when all treatment and interference with the breasts had been abolished. He felt that there should also be a minimum of fuss in the care of the new-born baby. Twenty-five years ago the babies were slung in a cot at the end of the bed. In the intervening years they had left that station and departed far from the mothers, but now after taking up all manner of stations they were once more back at the end of the bed.

Dr. A. White Franklin asked whether the three-hourly feeding programme for the babies was demanded by the babies themselves, left to their own devices by the "no touch" technique. 3 out of every 4 of the Queen Charlotte's babies were happy on four-hourly feeding, which saved considerable nursing time.

Dr. Franklin questioned the wisdom of a general stopping of silver nitrate prophylaxis in all countries, or in all parts of this country. Although gonococcal ophthalmia is a rarity in London and Cardiff, there would be a danger anywhere where women were still delivered with untreated gonorrhœa.

He suggested that the striking fall in mortality of the new-born in Professor Watkins' unit might be due to increased general interest in the details of the care of the babies as much as to any specific measures adopted, such as special clothes and "no touch".

Professor Watkins replied that the three-hourly interval was not the babies' choice. He thought three-hourly seemed to suit them best and quoted in support the opinions of Dr. Donald Paterson and Dr. C. A. Aldridge.

Dr. Beryl D. Corner said she was convinced that allowing mothers to do more for the babies and reducing all handling of the babies by the nursing staff to a minimum had reduced the incidence of minor sepsis in her maternity units.

Dr. V. Mary Crosse reminded the meeting that it was not so important to wash the baby as always to wash the hands before handling a baby.

Dr. Helen Mackay had found that when mothers in a maternity hospital were required as a routine measure to wear masks while feeding their babies, they mostly failed to grasp the correct technique and so the mask did not achieve its purpose. If a mother had an infection, her willing co-operation could usually be aroused and hence success often achieved. Fathers should be allowed to see their babies but asked to keep away if suffering from an infection.

She pointed out that means taken to combat cross-infection in different hospitals varied widely, and that unfortunately a comparison of results achieved by different methods was usually vitiated by differing standards as to what constituted an infection.

Dr. J. H. Moseley said that there were many maternity units where the ratio of nurses to babies was extremely low and quite inadequate according to the standards of teaching hospitals and other main hospitals. He deplored the present tendency for normal deliveries to take place in hospital.

Mr. Hujohn A. Ripman thought that whatever were the theoretical virtues of keeping the babies in the wards with their mothers, in practice it was certainly intolerable that this should be the case at night. Except in very small wards, the noise made by the new-born infants absolutely prohibited the mothers from getting any sleep. He, too, thought that as a general rule, whereas the father or the grandmother might be expected to wear a mask when looking at the child, to ask the mother to separate herself from her baby in this manner was unreasonable except when there was a clear indication such as an upper respiratory tract infection.

Mr. Ian Donald thought that the dangers from inadvertent handling of the nose through a mask could be minimized by using a mask constructed in two layers with a light sheet of paper between the layers.